

PCT

WORLD INTELLECTUAL
Property Organization

INTERNATIONAL APPLICATION PUBLISHED U



WO 9602530A1

(51) International Patent Classification 6 : C07D 401/00, 451/00, A01N 43/42		A1	(43) International Publication Date: 1 February 1996 (01.02.96)
(21) International Application Number: PCT/US95/08854		(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 17 July 1995 (17.07.95)			
(30) Priority Data: 277,810 20 July 1994 (20.07.94) US			
(60) Parent Application or Grant (63) Related by Continuation US 277,810 (CIP) Filed on 20 July 1994 (20.07.94)		Published <i>With international search report.</i> <i>With amended claims.</i>	
(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): GUO, Liangquin [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). YANG, Lihu [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(54) Title: PIPERIDINES AND HEXAHYDRO-1H-AZEPINES SPIRO SUBSTITUTED AT THE 4-POSITION PROMOTE RELEASE OF GROWTH HORMONE			
(57) Abstract			
<p>The present invention is directed to di- and tri-substituted piperidines, pyrrolidines and hexahydro-1H-azepines which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such di- and tri-substituted piperidines and pyrrolidines as the active ingredient thereof are also disclosed.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTION

PIPERIDINES AND HEXAHYDRO-1H-AZEPINES SPIRO
SUBSTITUTED AT THE 4-POSITION PROMOTE RELEASE OF
GROWTH HORMONE

5

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic 10 effects on the metabolic processes of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

15 A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine 20 (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone 25 releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth 30 hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of

- 2 -

the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal 5 spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are 10 still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone secretagogues with a benzo-lactam structure are disclosed in U.S. Patent 4,206,235. The instant compounds are non-peptide analogs for promoting the release of growth hormone which are stable in a variety 15 of physiological environments and which may be administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

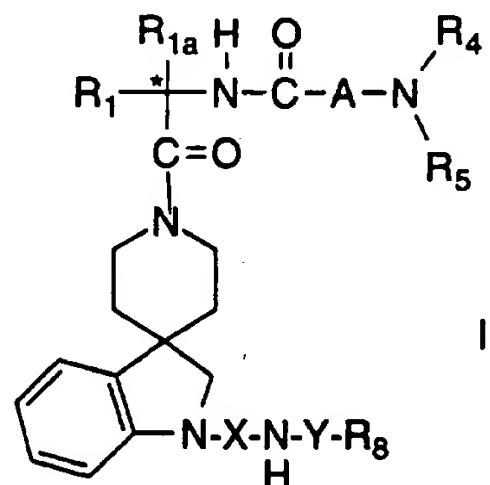
The instant invention covers certain piperidine and 20 hexahydro-1H-azepine compounds spiro substituted at the 4-position which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural 25 growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the piperidine and hexahydro-1H-azepine compounds spiro substituted at the 4-position. It is a further object of this invention to 30 describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the piperidine and hexahydro-1H-azepine compounds spiro substituted at the

- 3 -

4-position for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

5 DESCRIPTION OF THE INVENTION

The novel 4-spiro piperidines and hexahydro-1H-azepines of the instant invention are best described in the following structural formula I:



10 wherein:

R₁ is selected from the group consisting of:
 C₁-C₁₀ alkyl-, aryl-, aryl(C₁-C₆ alkyl)-,
 heteroaryl-, heteroaryl(C₁-C₆ alkyl)-,
 15 (C₃-C₇ cycloalkyl)-(C₁-C₆ alkyl)-,
 (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 aryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 heteroaryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and
 (C₃-C₇ cycloalkyl)-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl) -,
 20 wherein K is -O-, -S(O)_m-, -N(R₂)C(O)-, -C(O)N(R₂)-, -OC(O)-,
 -C(O)O-, -CR₂=CR₂- or -C≡C-,
 wherein R₂ and the alkyl groups are optionally further substituted with
 1 to 9 halo, -S(O)_mR_{2a}, 1 to 3 of -OR_{2a}, or -C(O)OR_{2a}, and wherein
 aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl,
 25 thiophenyl, furanyl, benzothiophenyl, benzofuranyl, pyridinyl,
 quinolinyl, triazolyl, imidazolyl, thiazolyl, and benzimidazolyl, wherein

- 4 -

aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C₁-C₆ alkyl, 1 to 3 of halo, 1 to 2 of -OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)(R₂), -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂),

5 -SO₂N(R₂)(R₂), -N(R₂)SO₂-aryl, or -N(R₂)SO₂R₂;

R_{1a} is hydrogen or C₁-C₄ alkyl;

R₂ is selected from the group consisting of:

10 hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl, wherein the alkyl or the cycloalkyl is unsubstituted or substituted with hydroxyl, C₁-C₃ alkoxy, thioalkyl, C(O)OR_{2a}, and wherein, if two -C₁-C₆ alkyl groups are present on one atom, the groups are optionally joined to form a C₃-C₈ cyclic ring optionally including oxygen, sulfur, 15 or NR_{2a}, the C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine;

R_{2a} is hydrogen or C₁-C₆ alkyl;

20 R₄ and R₅ are independently selected from the group consisting of: hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl where the substituents are selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-furyl, 25 C₁-C₆ alkoxycarbonyl, and -S(O)_m(C₁-C₆ alkyl); or wherein R₄ and R₅ may be taken together to form -(CH₂)_rL_a(CH₂)_s-, wherein L_a is -C(R₂)₂-, -O-, -S(O)_m- or -N(R₂)-, wherein r and s are independently 1 to 3, and R₂ is defined above;

30

- 5 -

A is:



wherein x and y are independently 0, 1, 2 or 3;

5 Z is -N(R9)- or -O-, wherein R9 is hydrogen or C₁-C₆ alkyl;
 R₁₀ and R_{10a} are independently selected from the group consisting of:
 hydrogen, -C₁-C₆ alkyl, trifluoromethyl, phenyl, and substituted C₁-C₆
 alkyl wherein the substituents are selected from the group consisting of:
 imidazolyl, phenyl, indolyl, naphthyl, p-hydroxyphenyl, -OR₂,

10 -S(O)_mR₂, -C(O)OR₂, -C₃-C₇ cycloalkyl, -N(R₂)(R₂), and
 -C(O)N(R₂)(R₂);
 or R₁₀ and R_{10a} are independently joined to one or both of R₄ and R₅
 groups to form an alkylene bridge between the terminal nitrogen and
 the alkyl portion of the R₁₀ or R_{10a} groups, wherein the bridge
 15 contains 1 to 5 carbons atoms;

R₈ is hydrogen, C₁-C₁₀ alkyl, phenyl, benzyl or diphenyl methyl
 wherein the phenyl, benzyl or diphenyl groups may be substituted by
 halo, methyl or OR₂;

20 X is SO₂ or CO; and
 Y is selected from a chemical bond, SO₂, CO, C(O)O, C(O)N(R₂), and
 SO₂ N(R₂);
 m is 0, 1, or 2; and
 25 n is 1 or 2;

and pharmaceutically acceptable salts and individual diastereomers
 thereof.

30 In the above structural formula and throughout the
 instant specification, the following terms have the indicated
 meanings:

The alkyl groups specified above are intended to include
 those alkyl groups of the designated length in either a straight or

- 6 -

branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propinyl, butadienyl, hexenyl and the like.

5 The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary 10 butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, propinyloxy, isobutenyloxy, hexenyloxy and the like.

The term "halo" or "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

15 The term "aryl" (unless otherwise specified) is intended to include phenyl and naphthyl. The term "heteroaryl" (unless otherwise specified) is intended to include aromatic residues of 5- and 6- membered rings with 1 to 3 heteroatoms or fused 5- or 6- membered bicyclic rings with 1 to 4 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heteroaryl include indolyl, 20 dihydroindolyl, thiophenyl, furanyl, benzothiophenyl, benzofuranyl, pyridinyl, pyrimidinyl, quinolinyl, triazolyl, imidazolyl, thiazolyl, tetrazolyl, and benzimidazolyl.

25 Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other, i.e. when any variable (e.g., alkyl, aryl, R₂, etc.) occurs more than one time within any variable or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

30 Preferred compounds of the instant invention include those of structural formula I wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl(C₁-C₄ alkyl)-,

C₅-C₆ cycloalkyl-(C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-C₁-C₂ alkyl-,

- 7 -

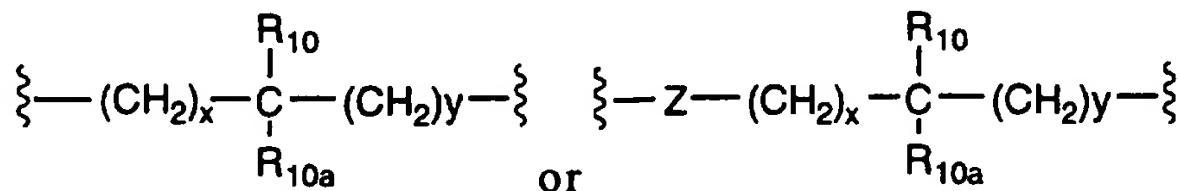
aryl(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-,
 C₃-C₆cycloalkyl(C₀-C₂alkyl)-K-(C₁-C₂alkyl)-, wherein K is O or
 S(O)_m, and the aryl is phenyl, or naphthyl and the heteroaryl is indolyl
 and the aryl and heteroaryl groups are optionally unsubstituted or
 5 substituted by 1 to 2 C₁-C₄ alkyl, 1 to 2 halo, OR₂, C(O)OR₂, CF₃ or
 S(O)_mR₂;

R₂ is selected from the group consisting of:
 hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, wherein the alkyl or the
 10 cycloalkyl is unsubstituted or substituted with hydroxyl, C₁-C₃ alkoxy,
 thioalkyl, C(O)OR_{2a}, and, if two C₁-C₆ alkyls are present on one atom,
 they may be optionally joined to form a C₅-C₆ cyclic ring optionally
 including the heteroatoms oxygen or NR_{2a}, the C₃-C₈ cyclic ring being
 selected from the group consisting of pyrrolidine, piperidine,
 15 piperazine, morpholine, thiomorpholine;

R_{2a} is hydrogen or C₁-C₄ alkyl;

R₄ and R₅ are independently selected from the group consisting of:
 20 hydrogen, C₁-C₄ alkyl, substituted C₁-C₄ alkyl where the substituents
 are 1 to 2 hydroxy or S(O)_m(C₁-C₃alkyl); or wherein R₄ and R₅ are
 optionally taken together to form (CH₂)_rN(R₂)(CH₂)_s wherein r and s
 are independently 1 to 3 and R₂ is defined above;

25 A is:



wherein x and y are independently 0,1 or 2;
 Z is -N(R₉)- or -O-, wherein R₉ is hydrogen or C₁-C₄ alkyl;
 30 R₁₀ and R_{10a} are independently selected from the group consisting of:

- 8 -

hydrogen, C1-C3 alkyl; or R10 and R10a are optionally independently joined to one or both of the R4 and R5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R10 or R10a groups to form 5 or 6 membered rings containing the terminal nitrogen;

X is SO₂;

Y is CO, CO₂, or SO₂;

R₈ is C₁-C₆ alkyl, phenyl or benzyl optionally substituted with halo,

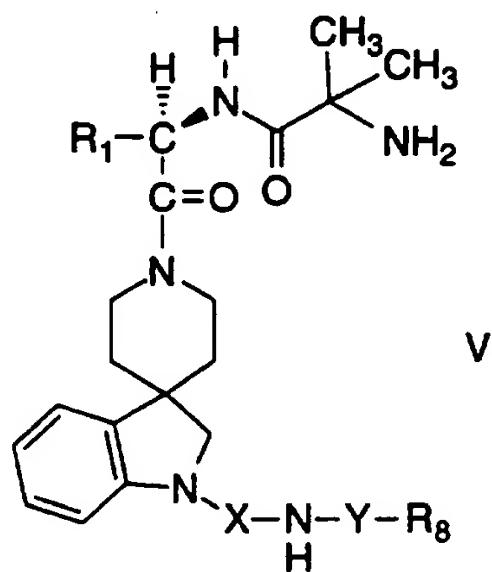
10 methyl or OR_2 ;

m is 0, 1, or 2; and

n is 1;

15 or their pharmaceutically acceptable salts and individual diastereomers
thereof.

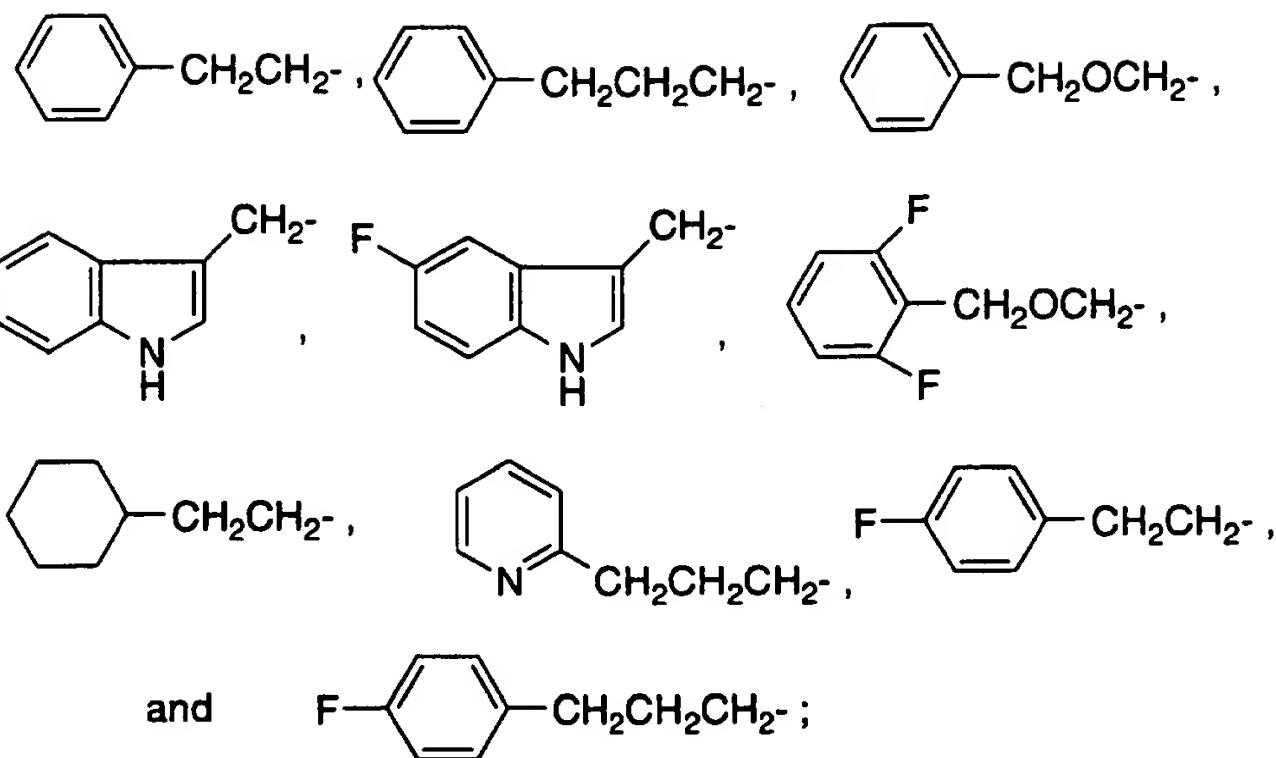
Most preferred compounds of the instant invention are realized in structural formula V:



20

wherein R1 is selected from the group consisting of:

- 9 -



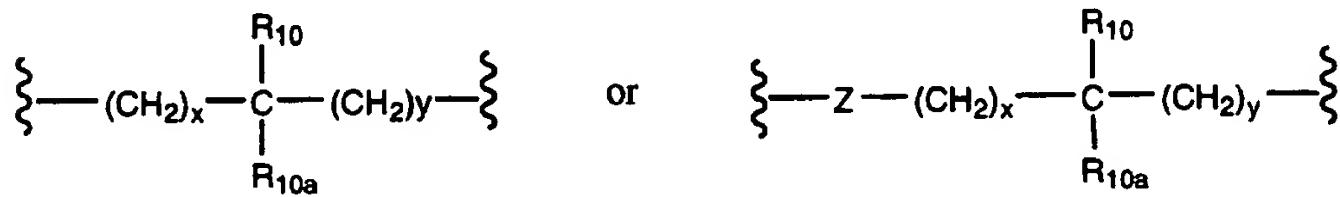
R_2 is selected from the group consisting of:
 hydrogen, C_1 - C_4 alkyl;

5

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, substituted C_1 - C_4 alkyl wherein the substituents are 1 to 2 hydroxy or wherein R_4 and R_5 are optionally taken together to form piperazine;

10

A is



15 wherein x and y are independently 0, 1 or 2;
 Z is $N(R_9)$ or $-O-$, wherein R_9 is hydrogen or methyl;
 R_{10} and R_{10a} are independently selected from the group consisting of hydrogen and C_1 - C_3 alkyl; or R_{10} and R_{10a} are optionally

- 10 -

independently joined to one or both of the R4 and R5 group to form pyrrolidine or piperidine rings;

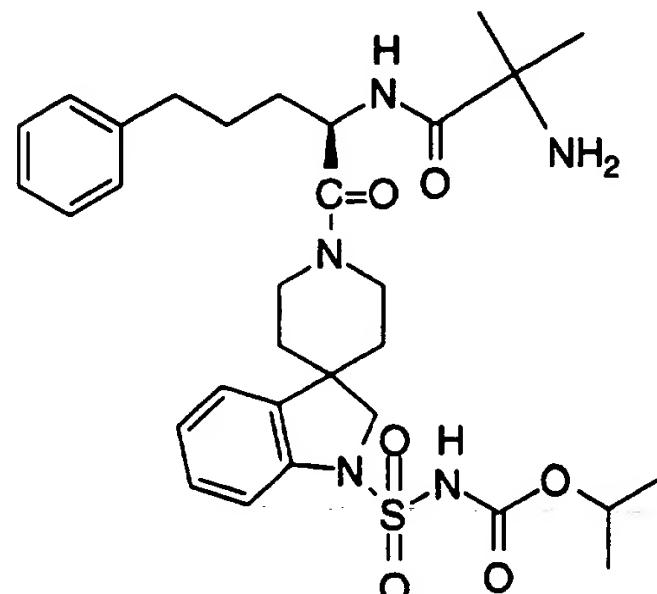
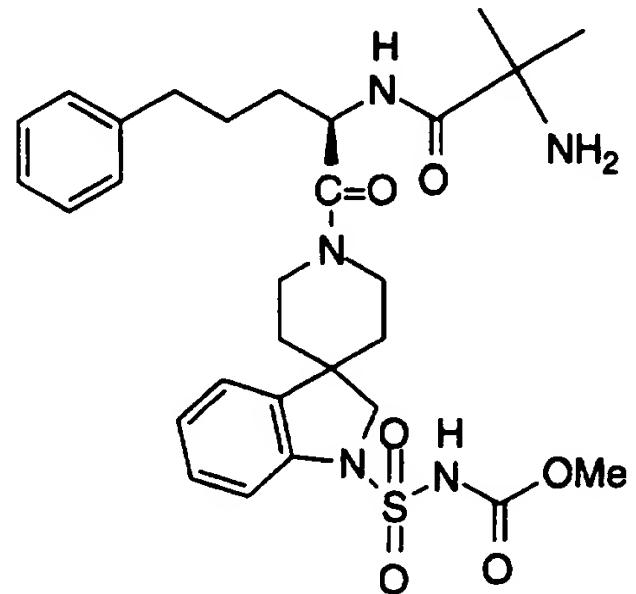
X is SO₂;

Y is CO or SO₂;

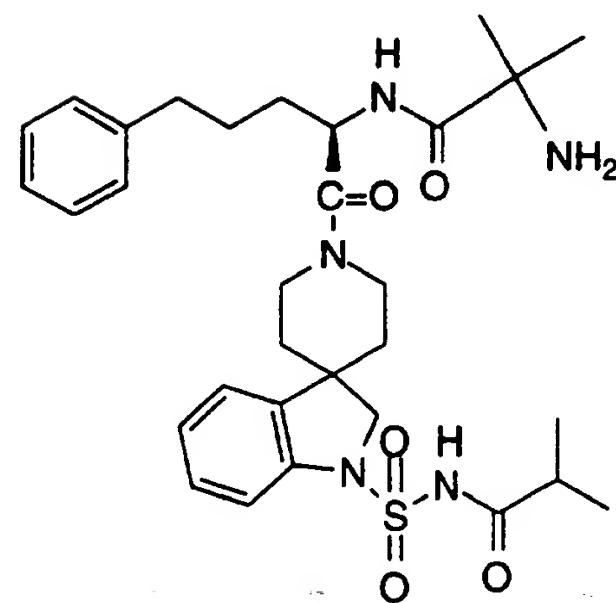
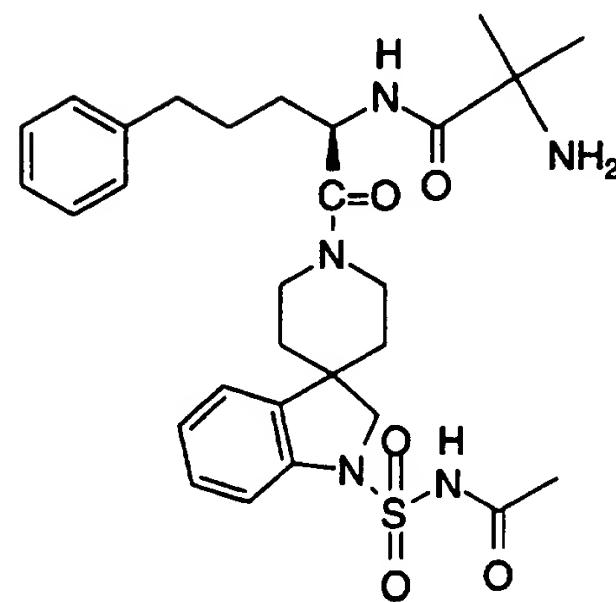
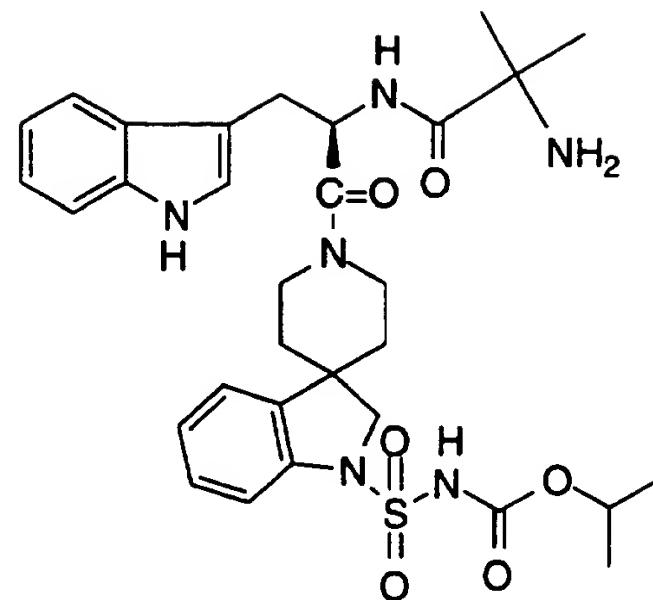
5 R₈ is hydrogen, C₁-C₄ alkyl, phenyl or benzyl optionally substituted by halo, methyl or OR₂; and
m is 0, 1, or 2;

10 and the pharmaceutically acceptable salts and individual diastereomers thereof.

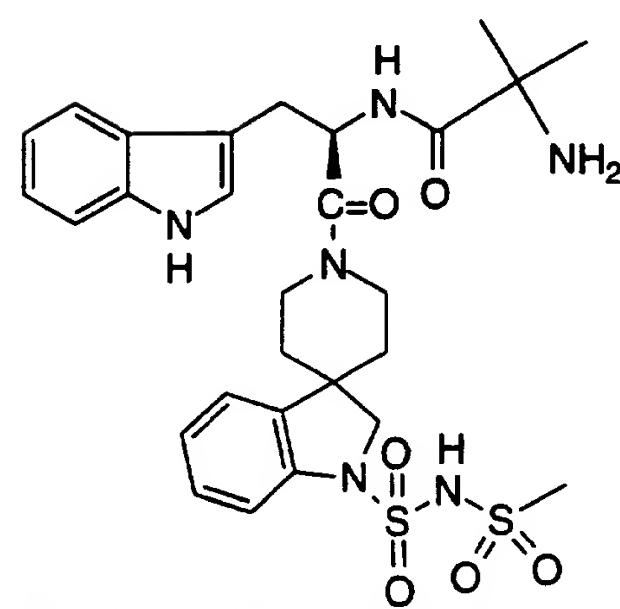
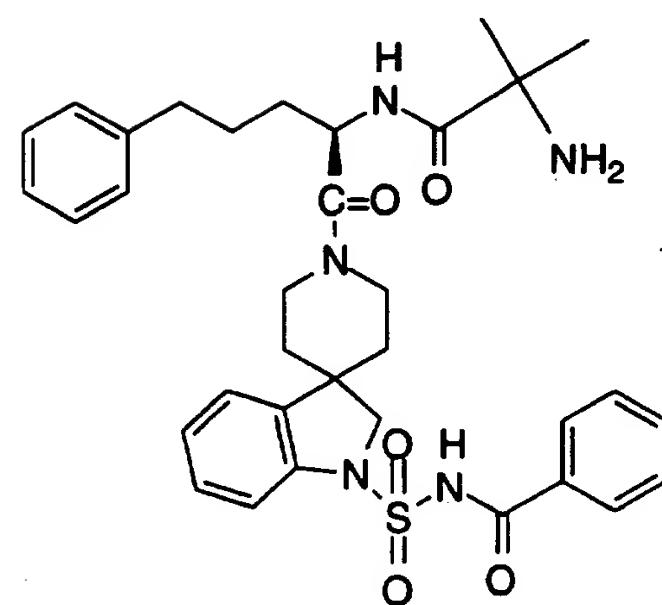
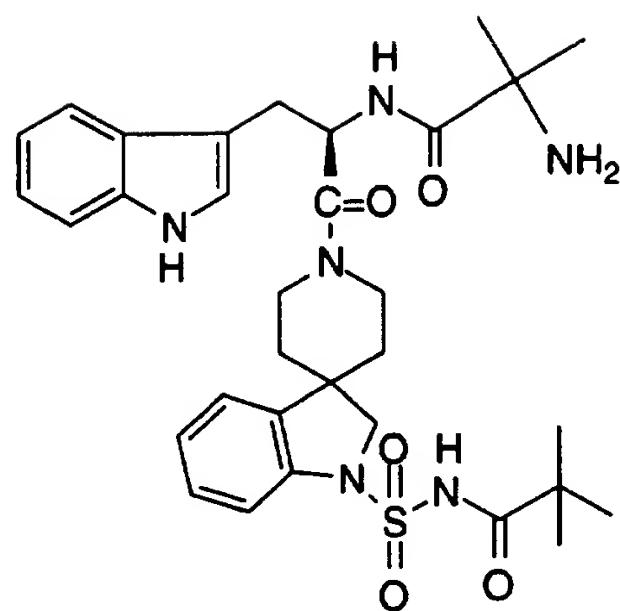
Representative most preferred growth hormone releasing compounds of the present invention include the following:



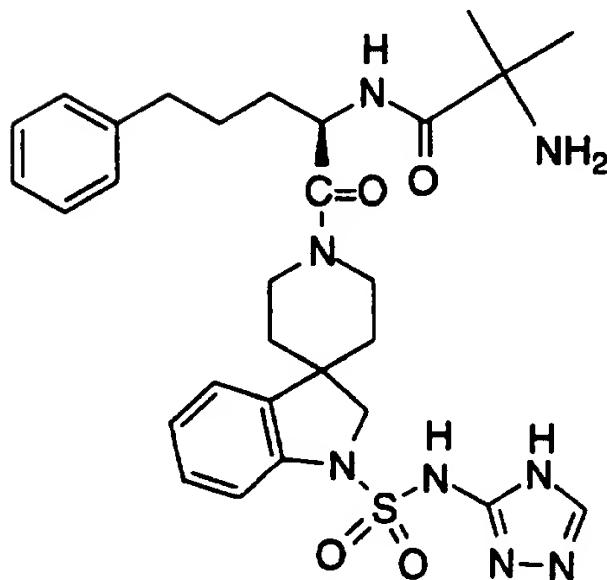
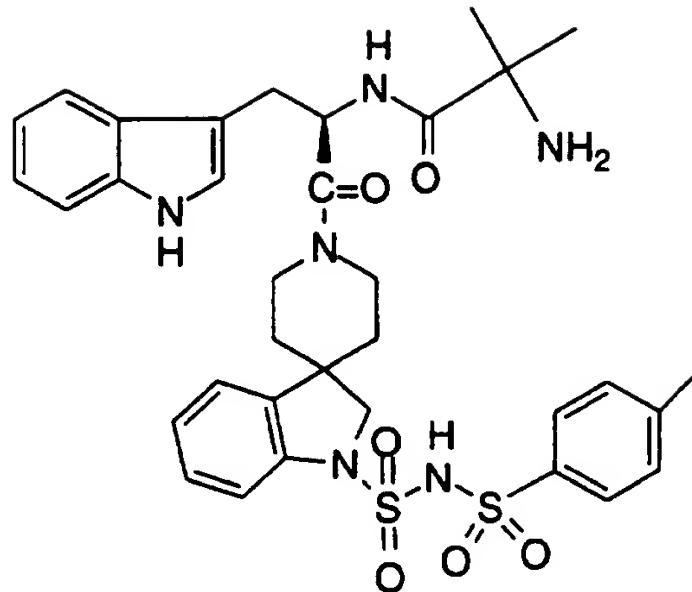
- 11 -



- 12 -



- 13 -



or a pharmaceutically acceptable salt thereof.

5 Throughout the instant application, the following abbreviations are used with the following meanings:

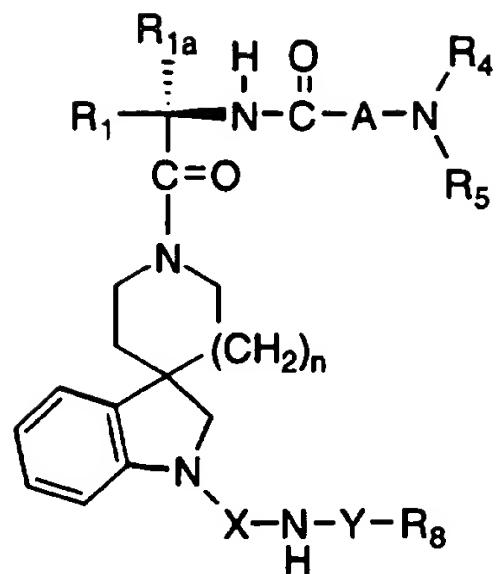
	BOC	t-butyloxycarbonyl
	BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
10	CBZ	Benzoyloxycarbonyl
	DIBAL-H	diisobutylaluminum hydride
	DMF	N,N-dimethylformamide
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride

- 14 -

	FAB-MS	Fast atom bombardment-mass spectroscopy
	GHRP	Growth hormone releasing peptide
	HOBT	Hydroxybenztriazole
5	LAH	Lithium aluminum hydride
	HPLC	High pressure liquid chromatography
	MHz	Megahertz
	MPLC	Medium pressure liquid chromatography
	NMM	N-Methylmorpholine
	NMR	Nuclear Magnetic Resonance
10	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TMS	Tetramethylsilane

15 The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two 20 optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the 25 absolute stereochemistry of the more active and thus more preferred isomer is as shown in Formula II in which R_{2a} is represented by a hydrogen. With the R_{1a} substituent as hydrogen, the special configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also designated an R-configuration 30 although this will vary according to the values of R₁ and R_{1a} used in making R- or S- stereochemical assignments.

- 15 -



Formula II

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as 5 the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy may be isolated in the form of their 10 inorganic salt in which the counterion may be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic 15 routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes in which R_{2a} is shown as H.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an 20 amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize the undesired reaction are

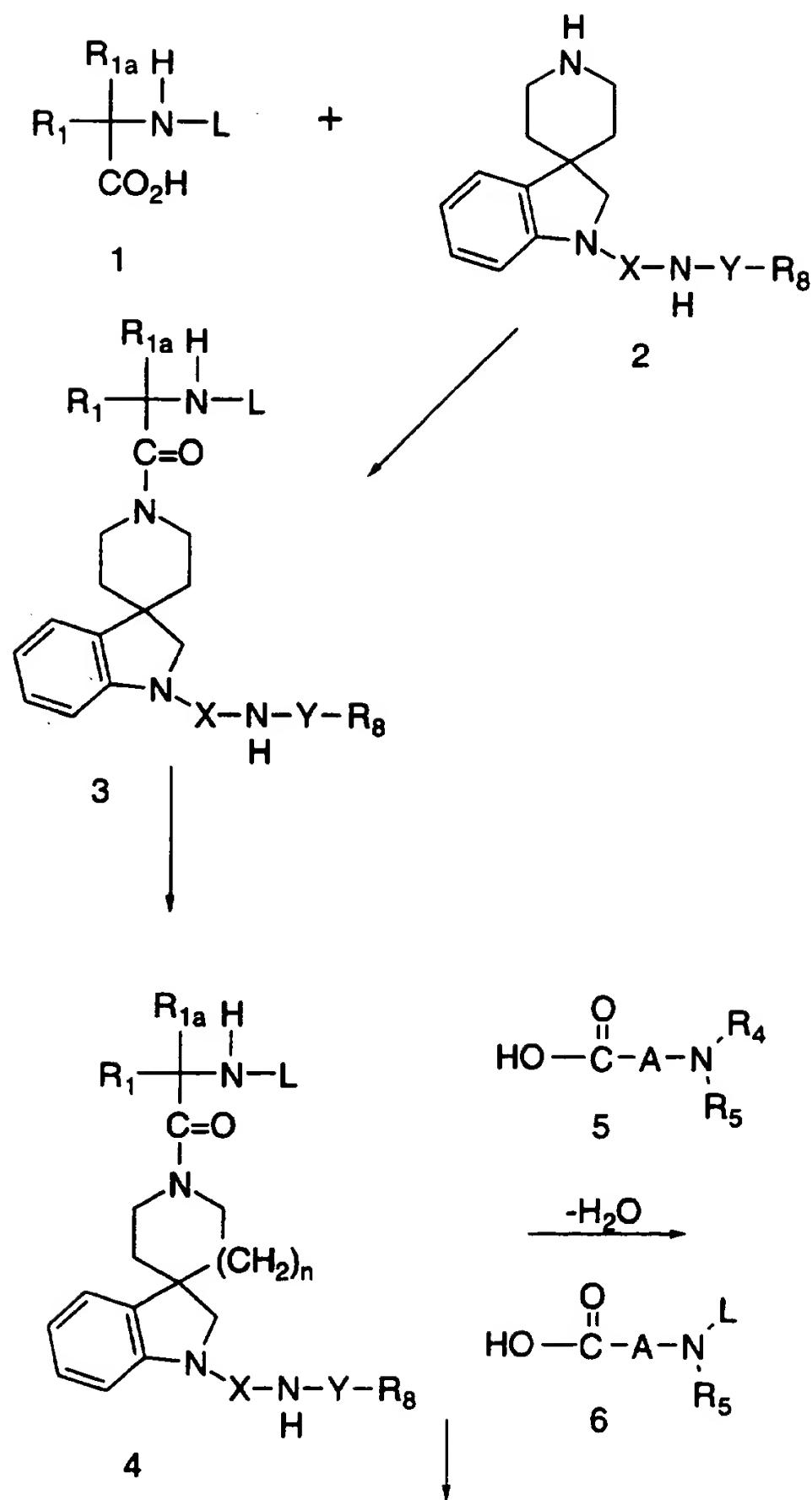
- 16 -

well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis,

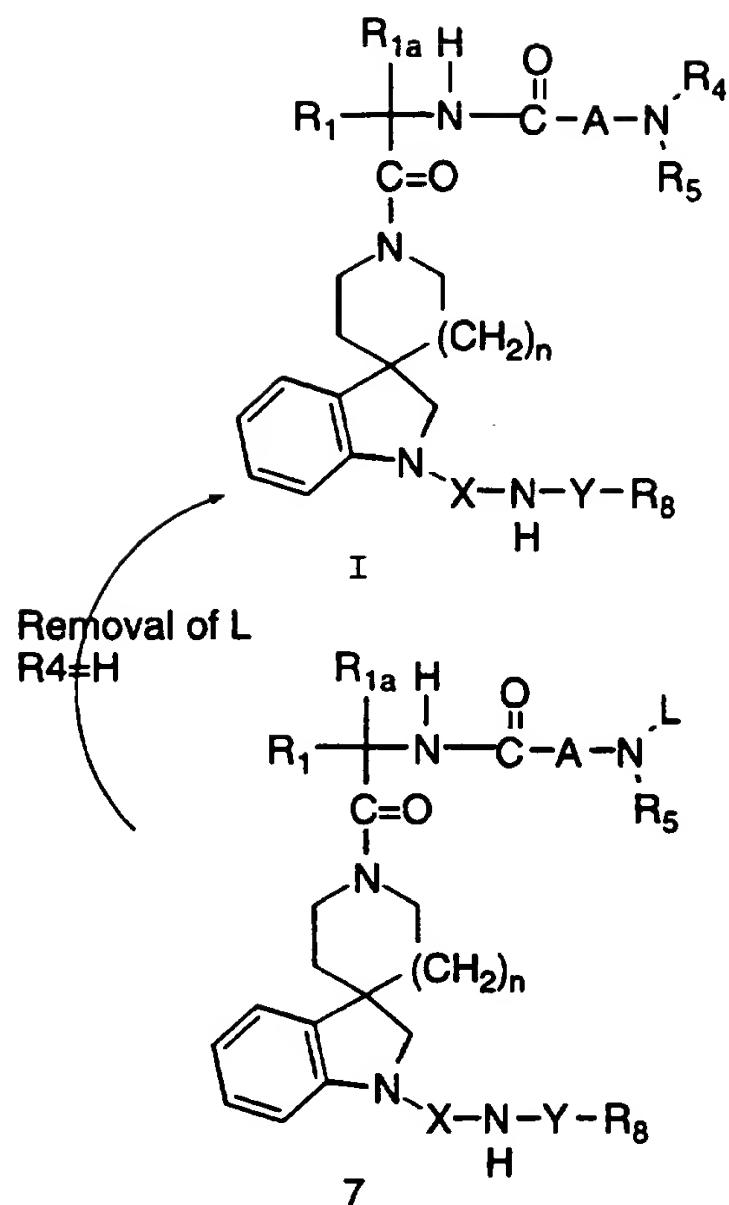
5 and their removal conditions are known to those skilled in the art. Removal of CBZ groups may be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic
10 hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups may also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene
15 chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 may be
20 prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α -Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperazines of formula 2 are either commercially available or known in the literature and others may be prepared following literature methods described for known compounds, some of which are described here. The
25 skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures includes crystallization, normal phase or reverse phase chromatography.

- 17 -

SCHEME 1

- 18 -



Coupling of the protected amino acids of formula 1, wherein L is a suitable protecting group, with amine of formula 2, whose preparations are described later, where X, Y and R8 are as defined above, is conveniently carried out under standard peptide coupling conditions to give intermediates of formula 3 as illustrated in Scheme 1. Conversion of 3 to intermediate 4 can be carried out as illustrated in the scheme by removal of the protecting group L (CBZ, BOC, etc.). Intermediates of formula 5, wherein A is connected to the carbonyl by a carbon atom and thus A is $-(\text{CH}_2)_x-\text{C}(\text{R}_7)(\text{R}_{7a})-(\text{CH}_2)_y$ can be prepared as shown in Scheme 1 by coupling intermediates of formula 4 to amino acids of formula 5 under the standard peptide coupling reaction conditions. The amino acids 5, as amino acid 1, are either commercially available or can be synthesized. Also if R4 or R5

5 defined above, is conveniently carried out under standard peptide coupling conditions to give intermediates of formula 3 as illustrated in Scheme 1. Conversion of 3 to intermediate 4 can be carried out as illustrated in the scheme by removal of the protecting group L (CBZ, BOC, etc.). Intermediates of formula 5, wherein A is connected to the carbonyl by a carbon atom and thus A is $-(\text{CH}_2)_x-\text{C}(\text{R}_7)(\text{R}_{7a})-(\text{CH}_2)_y$ can be prepared as shown in Scheme 1 by coupling intermediates of formula 4 to amino acids of formula 5 under the standard peptide coupling reaction conditions. The amino acids 5, as amino acid 1, are either commercially available or can be synthesized. Also if R4 or R5

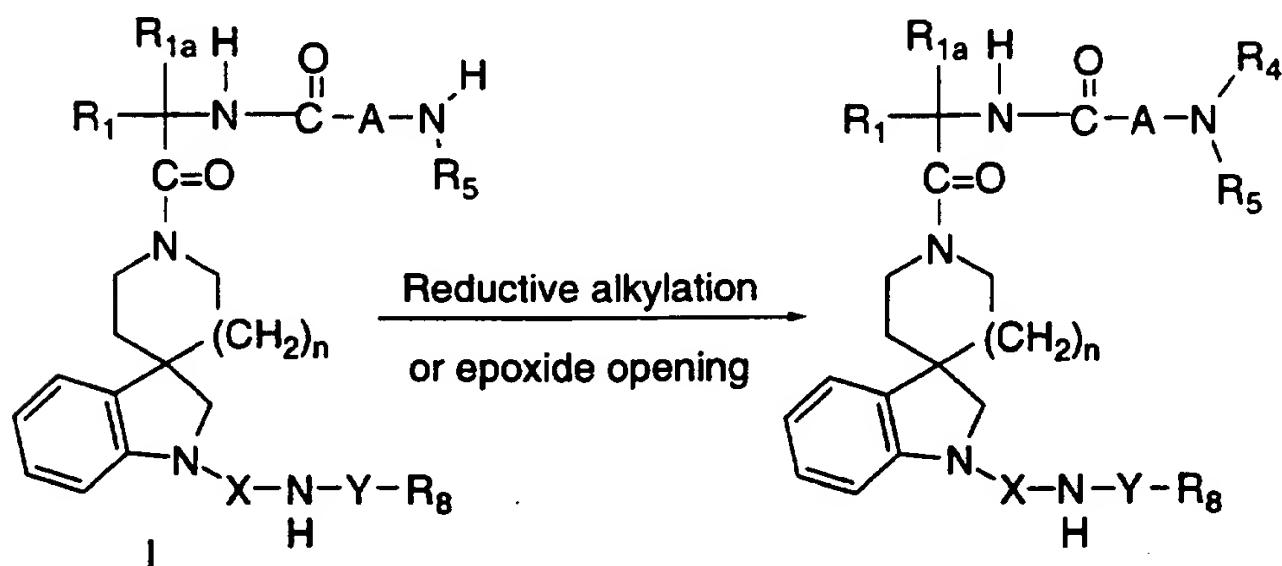
10

- 19 -

is a hydrogen then the protected amino acids **6** are employed in the coupling reaction, wherein L is a protecting group as defined above. The removal of L in **7** to afford **I**, where R₄=H, can be carried out under conditions known in the art.

5

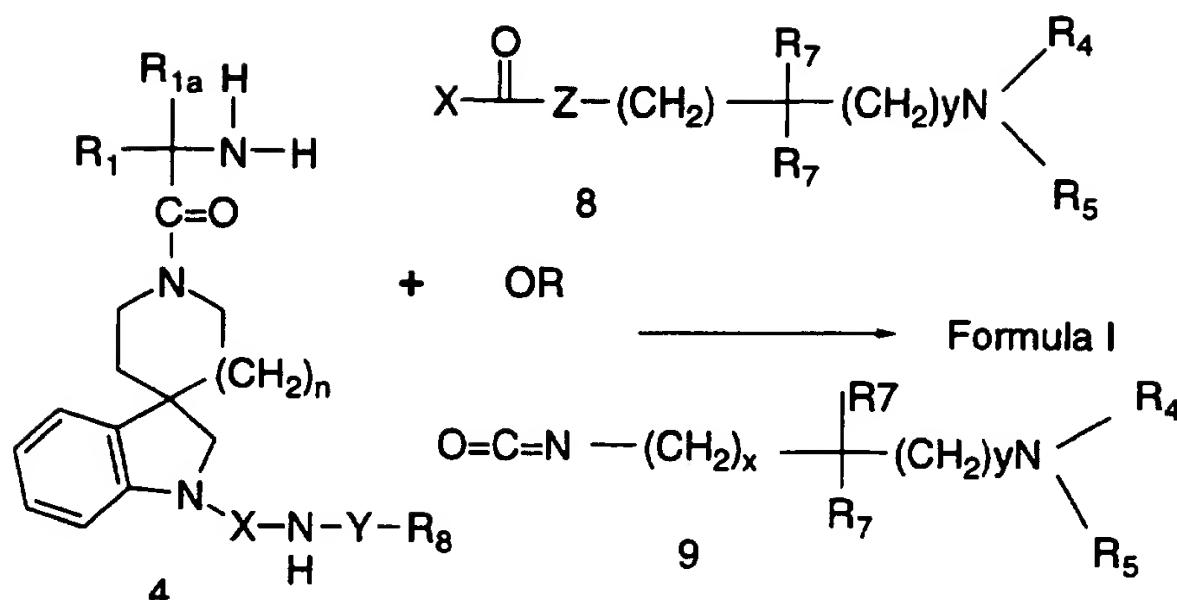
SCHEME 2



Compounds of formula **I** wherein R₄ and/or R₅ is a hydrogen can be further elaborated to new compounds **I** (with preferred side chains R₄ = CH₂-CH(OH)-CH₂X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 2. Reductive alkylation of **I** with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

- 20 -

SCHEME 3



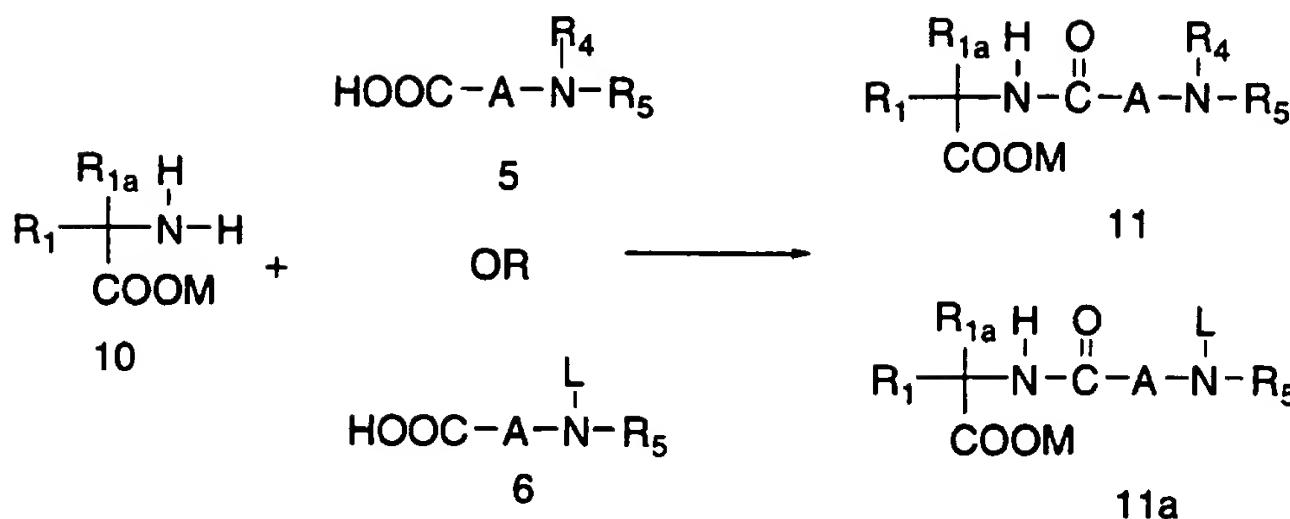
Compounds of formula I, wherein A is $Z-(CH_2)_x-$
 C(R_7)(R_7a)-(CH₂)_y and Z is N- R_6 or O can be prepared as shown in
 5 Scheme 3 by reacting 4 with reagents 8, wherein X is a good leaving
 group such as Cl, Br, I, or imidazole. Alternatively, 4 can be reacted
 with an isocyanate of formula 9 in an inert solvent such as 1,2-
 dichloroethane to provide compounds of formula I where Z is NH.

10 The compounds of general formula I of the present
 invention can also be prepared in a convergent manner as described in
 reaction Schemes 4, 5 and 6.

15 The carboxylic acid protected amino acid derivatives 10
 are, in many cases, commercially available where M = methyl, ethyl, or
 benzyl esters. Other ester protected amino acids can be prepared by
 classical methods familiar to those skilled in the art. Some of these
 methods include the reaction of the amino acid with an alcohol in the
 presence of an acid such as hydrochloric acid or p-toluenesulfonic acid
 and azeotropic removal of water. Other syntheses include the reaction
 20 of a protected amino acid with a diazoalkane, or with an alcohol and an
 acid activating agent such as EDC, DCC in the presence of a catalyst
 such as DMAP and removal of the protecting group L.

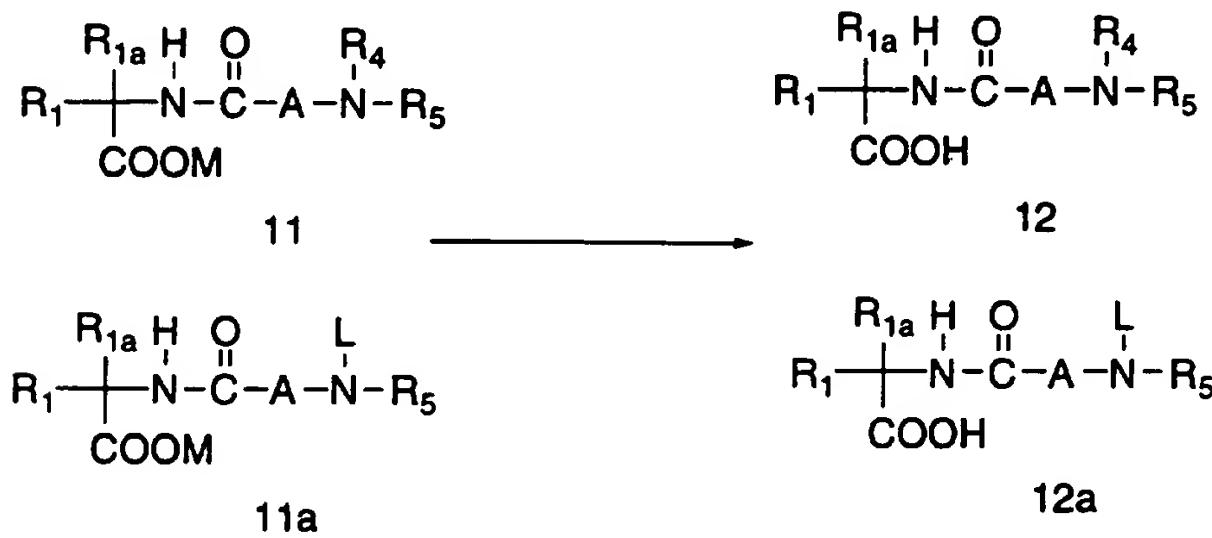
- 21 -

SCHEME 4



Intermediates of formula 11 or 11a, can be prepared as shown in Scheme 4 by coupling of amino acid ester 10 to amino acids of formula 6 or 7. When a urea or carbamate linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 3.

SCHEME 5

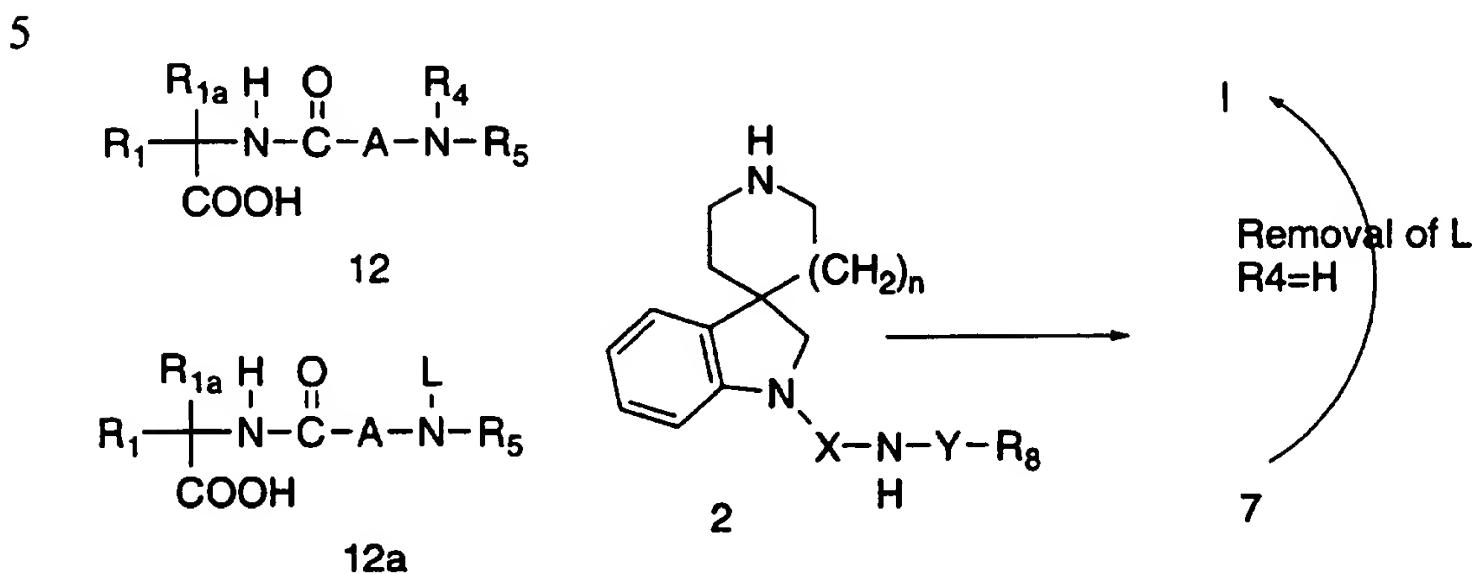


Conversion of the ester 11 or 11a to intermediate acids 12 or 12a can be achieved by a number of methods known in the art as described in Scheme 5; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis(triphenylphosphine) palladium catalyst in the

- 22 -

presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.* **1982**, *42*, 587).

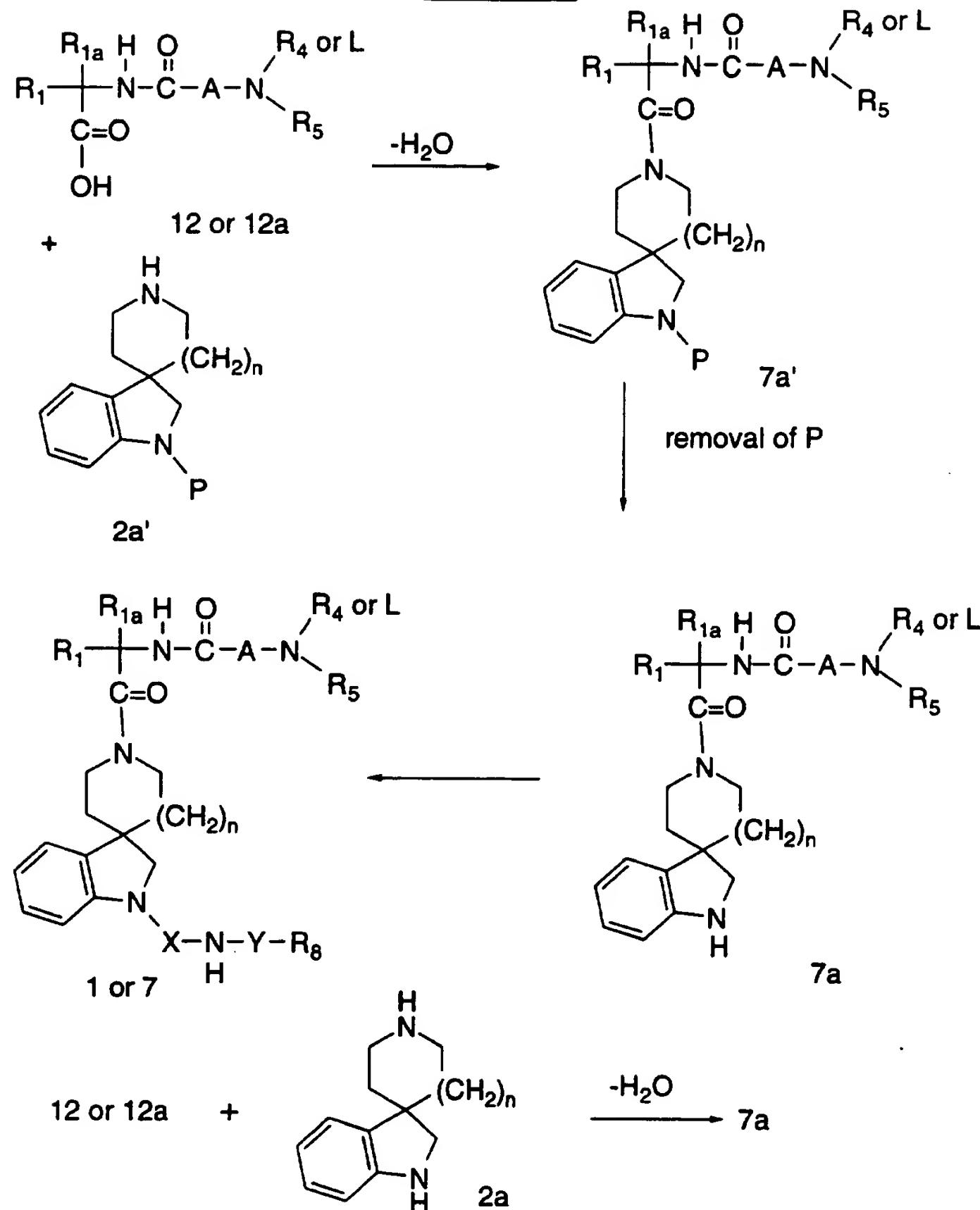
SCHEME 6



Acid **12** or **12a** can then be elaborated to **I** or compound **7** as described in Scheme 6. Coupling of compounds of formula **2** to acids of formula **12** or **12a**, wherein L is a suitable protecting group, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of **7** to **I** is achieved by removal of the protecting group L. When R₄ and/or R₅ is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

15

- 23 -

SCHEME 7

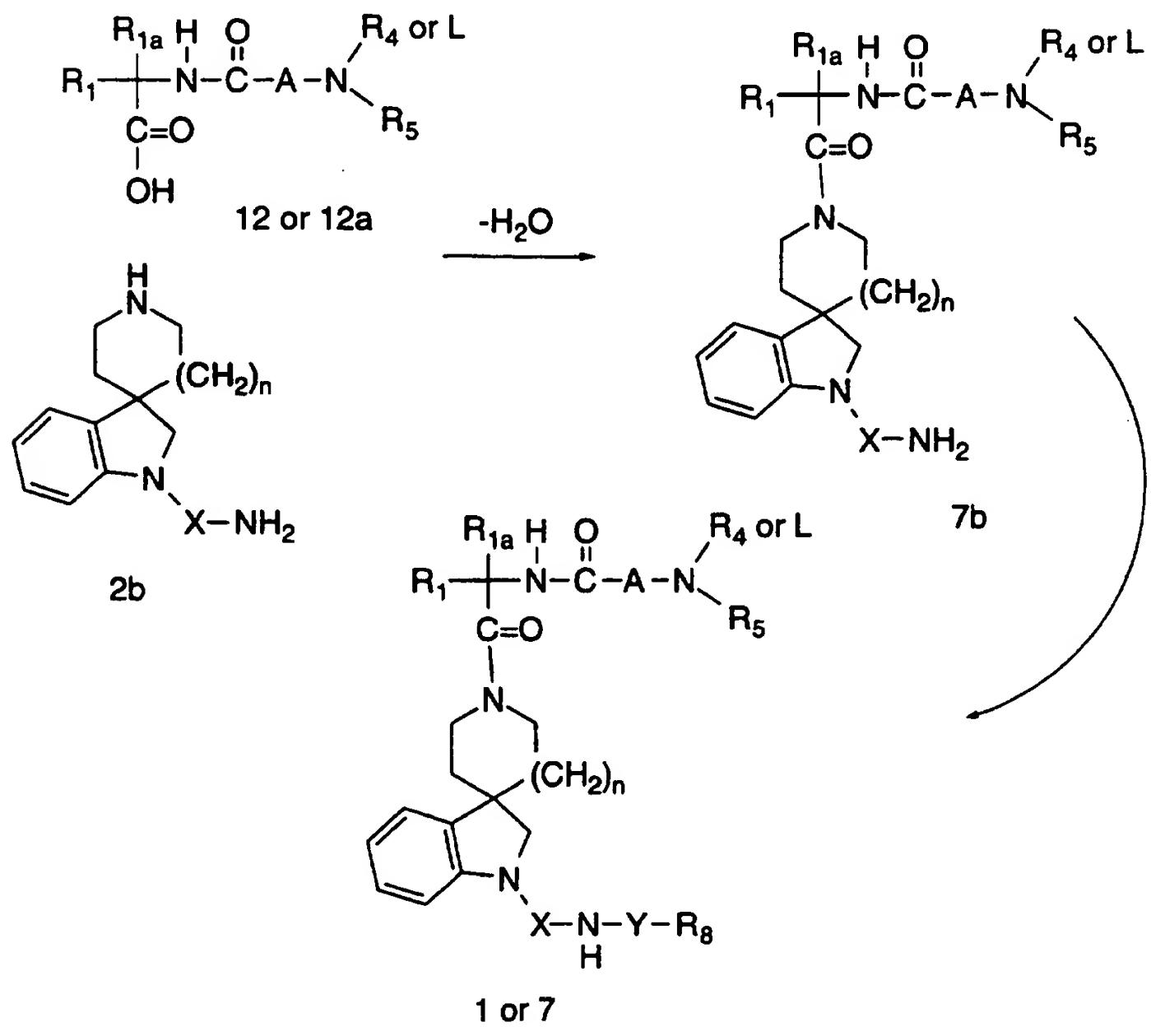
5

An alternative way of preparing compounds of structure I can be achieved through coupling reaction of 12 or 12a with spiroindoline 2a' (H. Ong *et al* *J. Med. Chem.* 1983, 23, 981-986), with P is a protecting group, under the standard peptide coupling reactions.

- 24 -

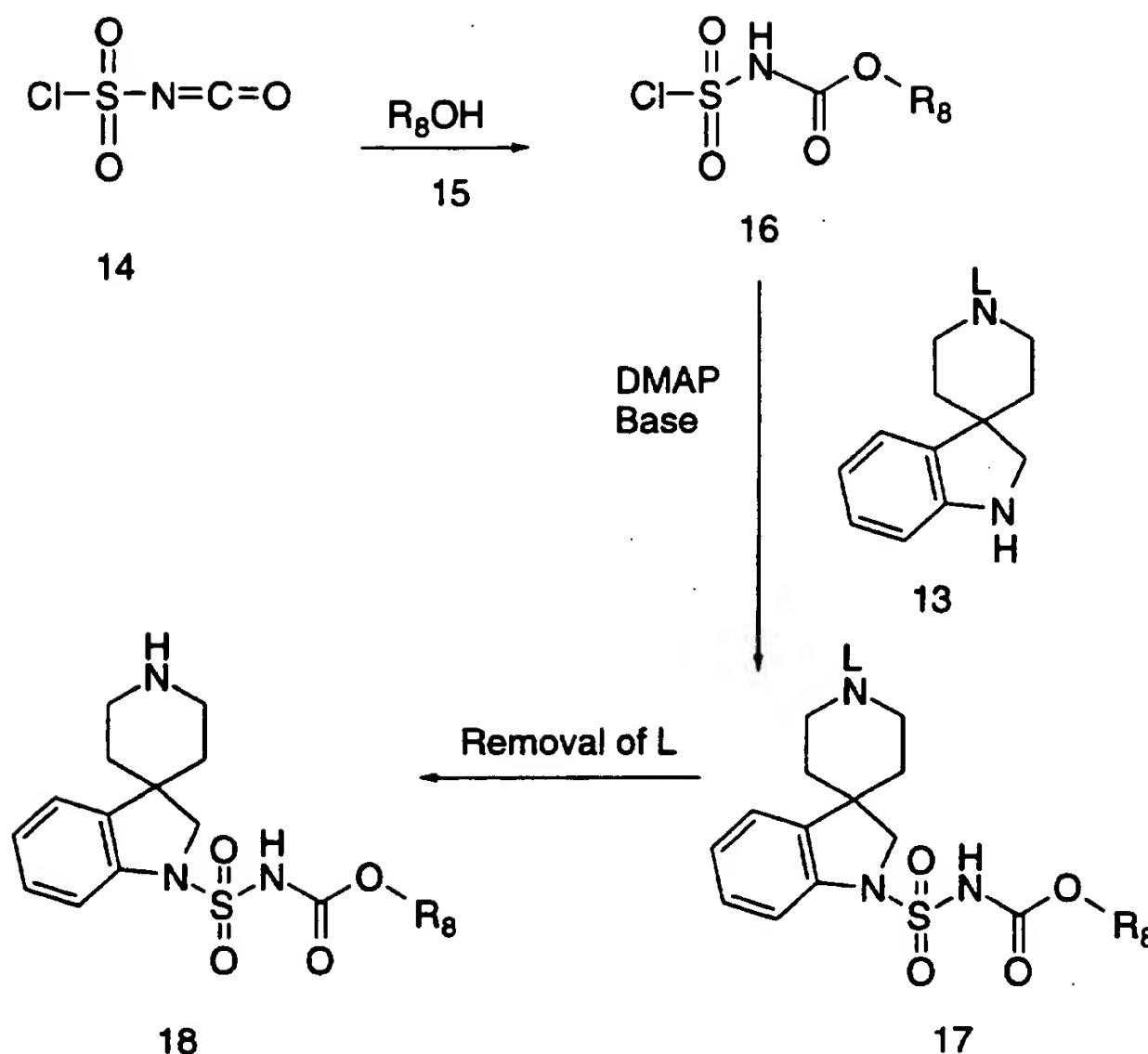
Then, removal of the protecting group at the indoline nitrogen and the functionalities attached to this position can be introduced according to the established procedures some of which are described later in this patent. Alternatively, compounds **12** or **12a** can be coupled directly with the unprotected spiroindoline **2a** selectively at the piperidine position to yield compound **7a**.

SCHEME 8



Alternatively, the acid **12** or **12a** can be coupled to the spirocompounds **2b** under the standard peptide coupling to give intermediates **7b**, which could be further elaborated to yield compound **1** or **7** under conditions described later.

- 25 -

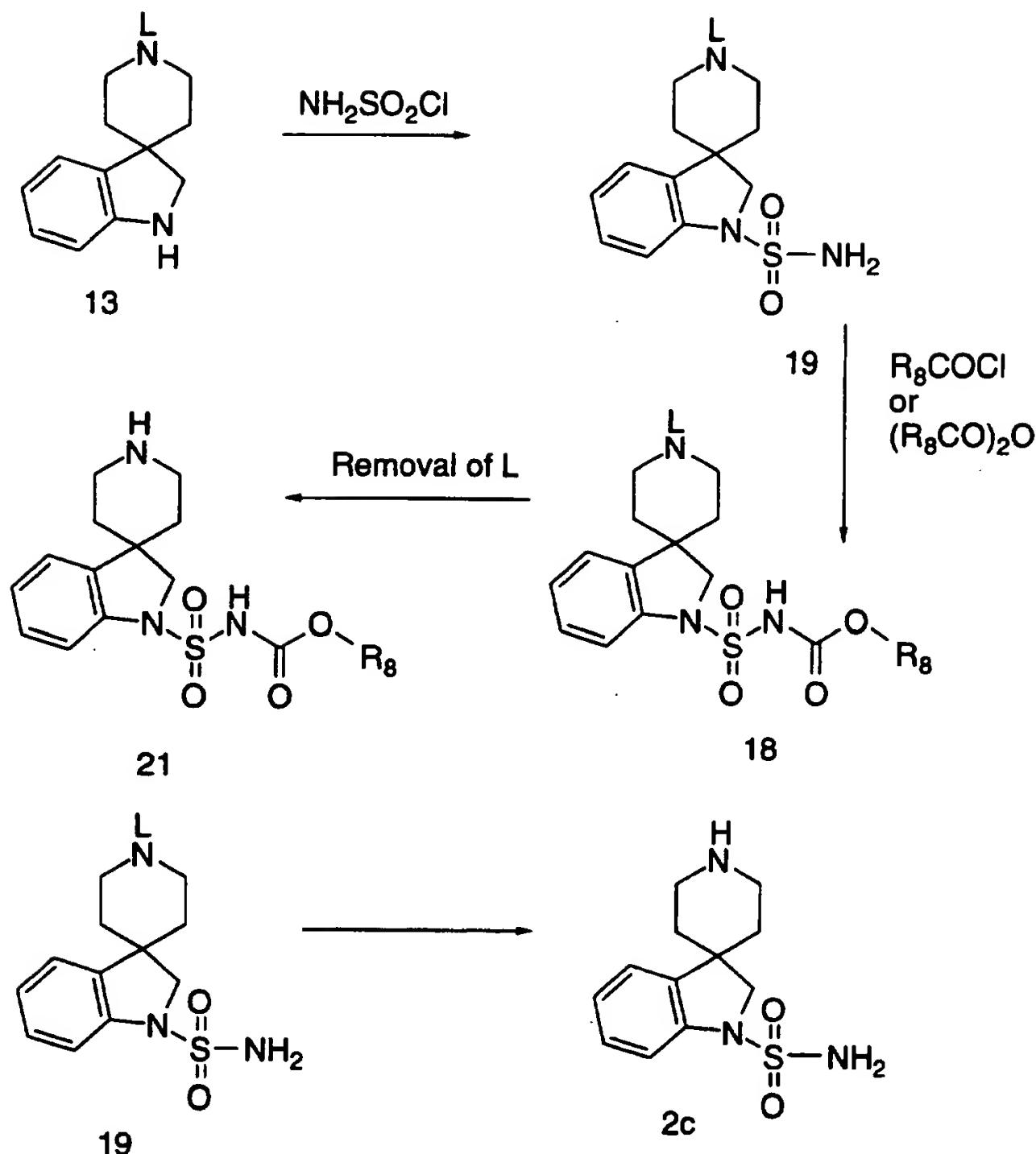
SCHEME 9

5 The spiroindolines **13**, where **L** is a protecting group such as CBZ, BOC can be prepared by procedures known in the literature (for example H. Ong *et al* *J. Med. Chem.* 1983, 23, 981-986). The reaction between chlorosulfonyl isocyanate and an alcohol **15**, where **R₈** is defined as above, to give a (chlorosulfonyl) carbamate **16** is well documented (see Burgess *et al* *Organic Systemses* vol. **VI**, 788).

10 Treatment of the spiroindoline **13** with the (chlorosulfonyl) carbamate **16** in the present of a base such as triethylamine or NMM and a catalyst such as DMAP gives the alkyl carboxysulfamide **17**. Removal of the protective group **L** under appropriate conditions affords the piperidine compound **18**, an example of compounds of general formula **2**.

- 26 -

SCHEME 10



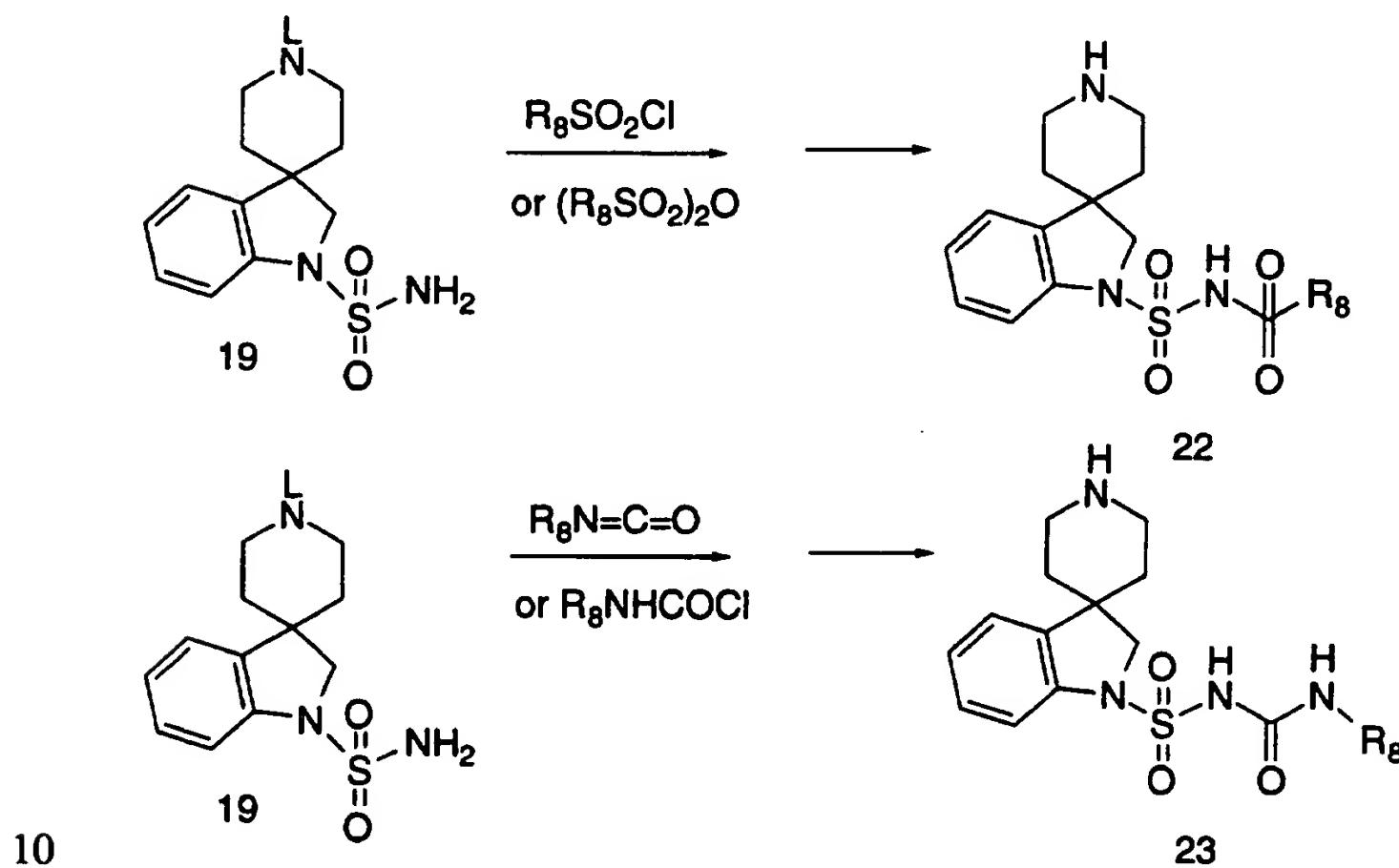
As shown in Scheme 10, reaction of the indoline 13 with 5 chlorosulfamide (*J. Org. Chem.* 54, 5825, 1989) in the presence of a base such as NMM gives the sulfamide 19. Acylation of the resulting sulfamide 19 with acyl chloride or anhydride in the presence of base such as triethylamine or NMM and catalytic amount of DMAP gives the acyl sulfamide 20. The acyl sulfamide 20 can also be prepared by reaction of 19 with a carboxylic acid $\text{R}_8\text{CO}_2\text{H}$ in the presence of a 10

- 27 -

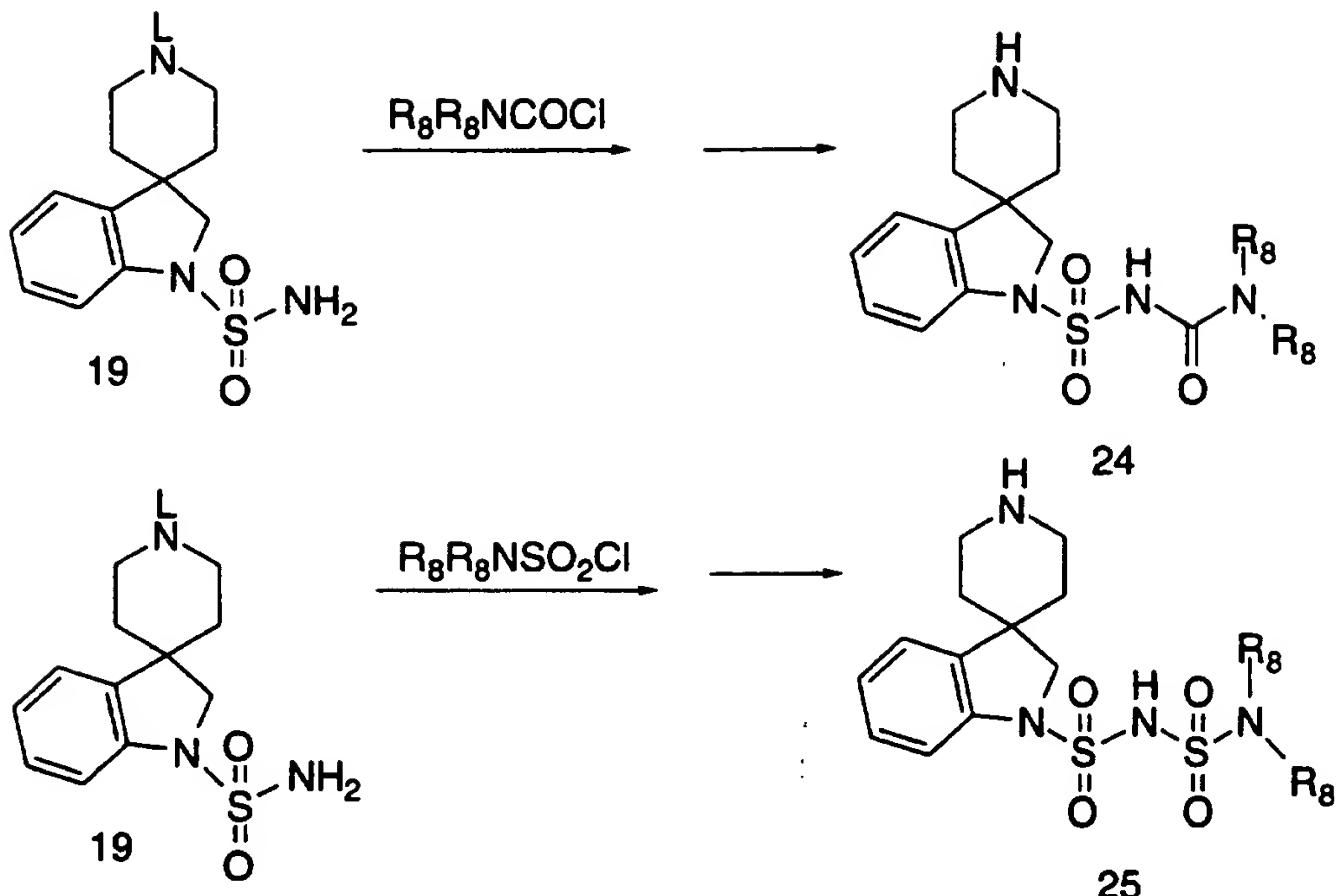
carboxylic acid activating reagent such as EDC, DCC and a catalyst such as DMAP. It is noted that the reaction described here can be also used in the advanced intermediates 7a shown in Scheme 7.

5 Removal of the protecting group L gives compound 21, an example of compounds of general formula 2. Removal of L in compound 19 gives piperidine 2c, an example of compound 2b (Scheme 8).

SCHEME 11

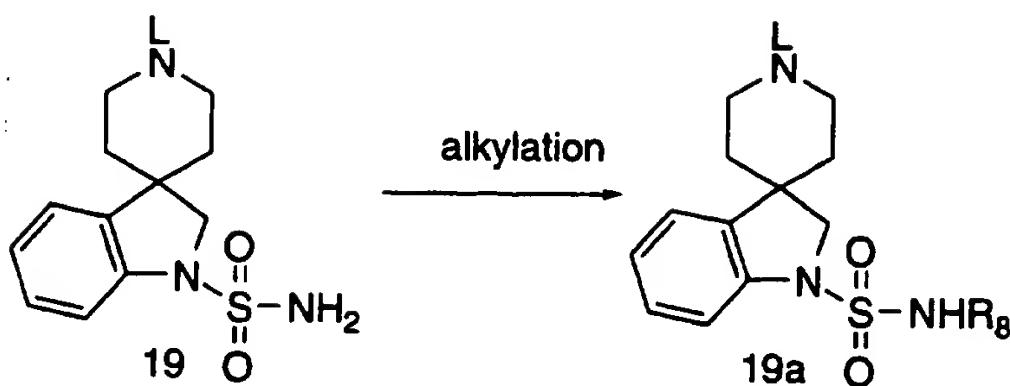
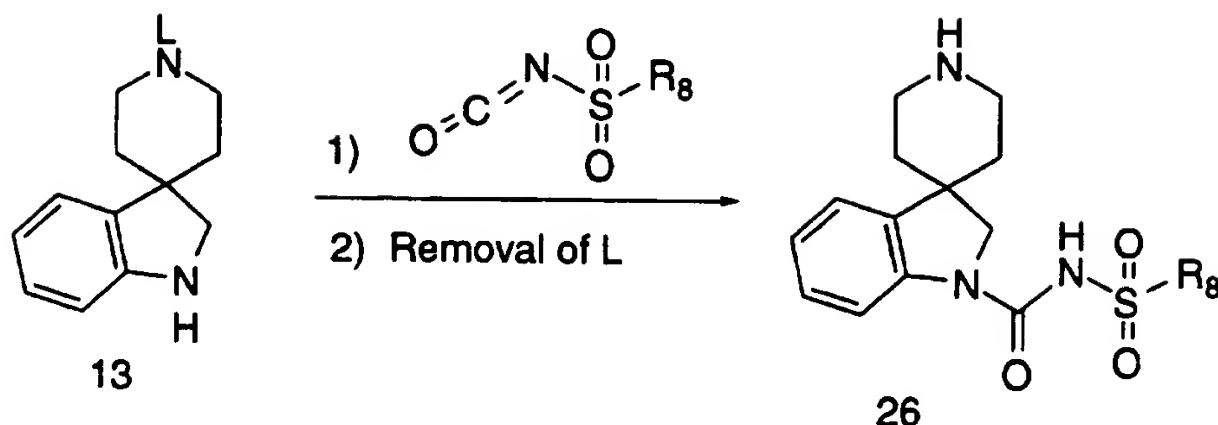


- 28 -



As shown in Scheme 11, the sulfonyl sulfamide **22** can be prepared similarly by reaction of compound **19** with a sulfonyl chloride or sulfonyl anhydride followed by removal of L. The carbamyl sulfamide **23**, **24** can be prepared by reaction of compound **19** with a carbamyl chloride or isocyanate respectively followed by removal of L. The sulfamyl sulfamide **25** can be prepared by reaction of compound **19** with a sulfamyl chloride (Matier and Conmer *J. Med. Chem.* 1972, 15, 538) under the same conditions. It is noted that these reaction schemes described here can be also used with the advanced intermediates **7b** shown in Scheme 8.

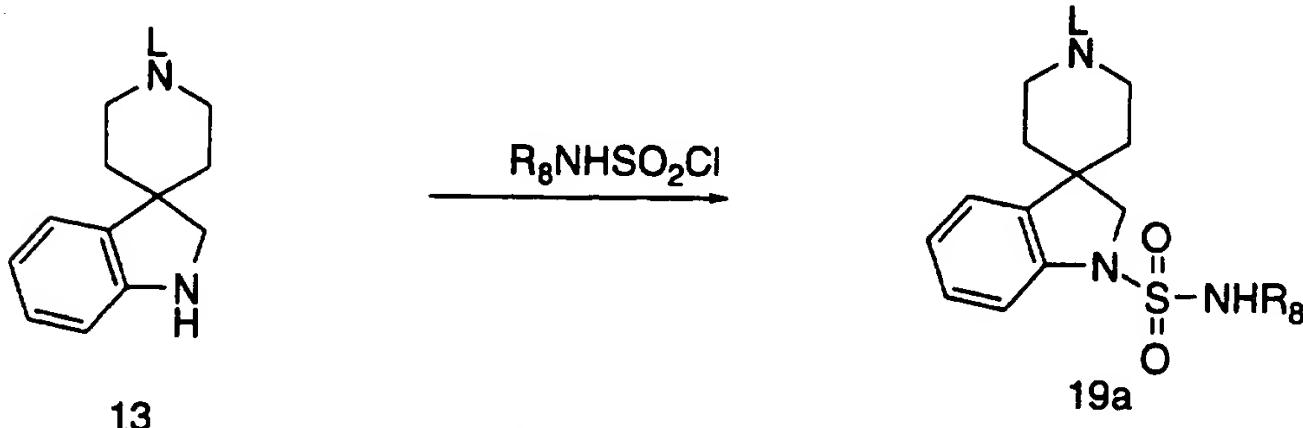
- 29 -

SCHEME 12

5

Reaction of compound 13 with sulfonyl isocyanate gives the sulfonyl urea 26 after removal of the protecting group L. It is noted that the reaction can be also used with the advanced intermediates 7a shown in Scheme 7.

10

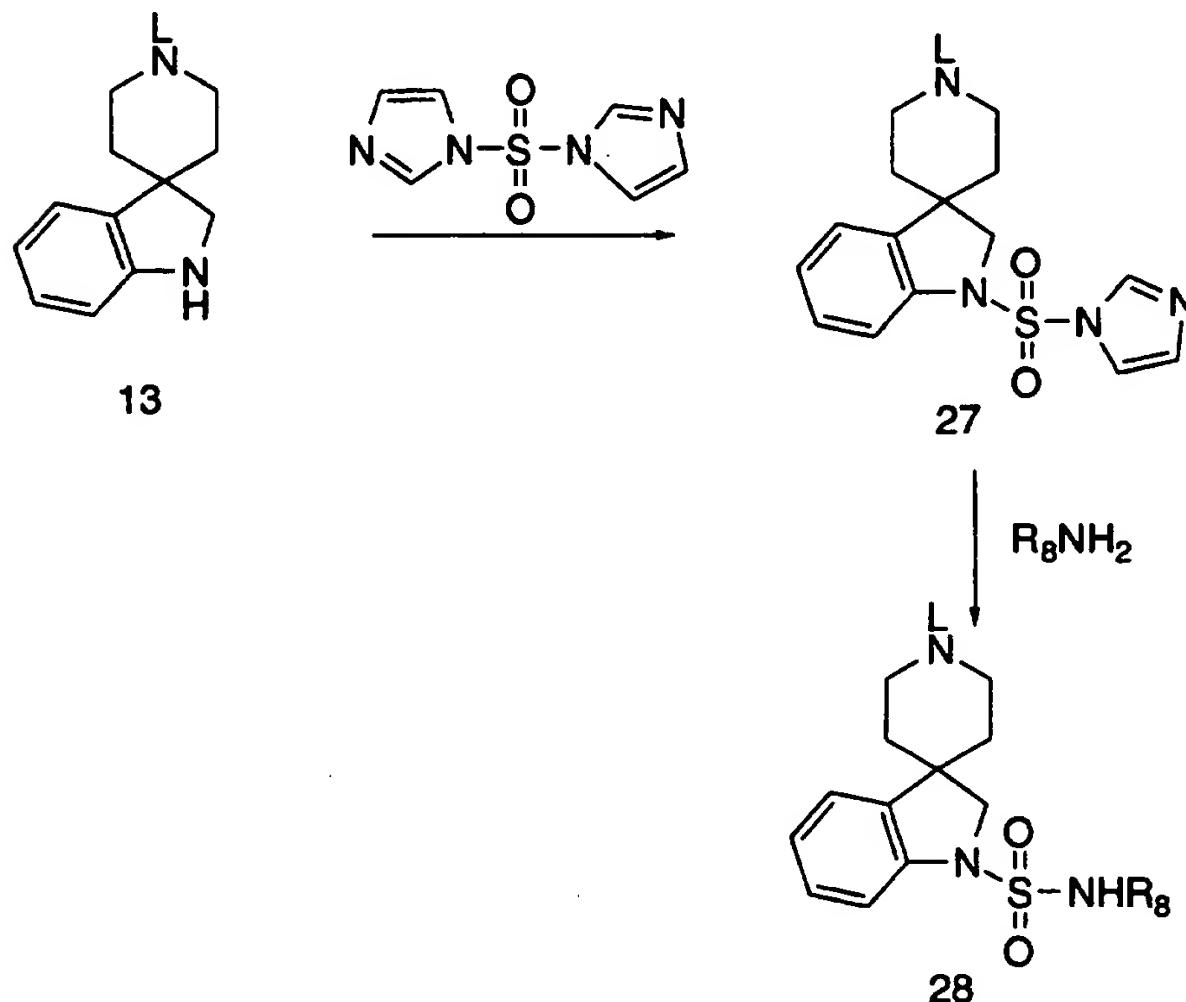
SCHEME 13

- 30 -

Substituted sulfamide or urea such as compound **19a** can be prepared from intermediate **19** by alkylation with an alkyl or aryl alkyl halide or other activated alkyl groups using a base such as sodium hydride in an inert solvent such as THF or DMF. Removal of the protective group L gives the piperidine ready for further reaction. It is noted that this reaction can also be carried out on advanced intermediates such as compound **7b**.

10

SCHEME 14



Alternatively, the substituted sulfamide can also be prepared by reaction of the indoline **13** with a substituted sulfamoyl chloride, which is either commercially available or can be conveniently prepared by procedures in the literature (for example J. A. Kloek and K. L. Leschinsky *J. Org. Chem.*, Vol. 41, No. 25, 1976, 4028-4029; W. L. Matier & W. T. Comer *J. Med. Chem.* 1972, vol 15, No. 5 538-

541), while the substituted ureas can be prepared by reaction of compound 13 with isocyanate. Removal of the protective group L gives the piperidine which may be employed in further reactions.

5 The sulfamide or the urea can also be prepared by reaction of compound 13 with 1,1'-sulfonyldiimidazole or 1,1'-carbonyl-diimidazole followed by reaction with amines R₈NH₂ to yield sulfamide of structure 28 or the urea analog. Removal of the protective group L gives the piperidine ready for further reaction. It is noted that these reactions can also be carried out on advanced intermediates such as 7a.

10 It is noted that the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

15 The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, *et al.*, *Science*, 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, the intrinsic growth hormone secretagogue activities of the compounds of the present invention may be demonstrated by this assay. The compounds of the following examples have activity in the 20 aforementioned assay in the range of 0.1 nm to 5 μ m.

25 The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits 30 growth hormone release and that the growth hormone releasing factor (GRF) stimulates its release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and

- 32 -

norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neuropeptides; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be

5 employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth
10 hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and

15 increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be
20 administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

25 Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition
30 to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth retardant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically

- 33 -

active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β -agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeronol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox, or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the compounds of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α -adrenergic agonists such as clonidine or serotonin 5HT1D agonists such as sumatriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. In particular, the compounds of this invention may be used in combination with growth hormone releasing factor, an analog of growth hormone releasing factor, IGF-1, or IGF-2. For example, a compound of the present invention may be used in combination with IGF-1 for the treatment or prevention of obesity. In addition, a compound of this invention may be employed in conjunction with retinoic acid to improve the condition of musculature and skin that results from intrinsic aging.

The present invention is further directed to a method for the manufacture of a medicament for stimulating the release of growth hormone in humans and animals comprising combining one of the compounds of the present invention with a pharmaceutical carrier or diluent.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of

- 34 -

stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses may be summarized as follows: treating growth hormone deficient adults;

- 5 prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness;
- 10 treating obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal
- 15 dysplasia, treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrody-splasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of
- 20 protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant
- 25 treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development and prevention of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination;
- 30 increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; treatment of syndromes manifested by non-restorative sleep and

- 35 -

musculoskeletal pain, including fibromyalgia syndrome or chronic fatigue syndrome; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and 5 cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and 10 improving the carcass quality of livestock. Likewise, the instant compounds are useful in a method of treatment of diseases or conditions which are benefited by the anabolic effects of enhanced growth hormone levels that comprises the administration of an instant compound.

15 In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone 20 deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

25 In addition, the instant compounds may be useful in the treatment of illnesses induced or facilitated by corticotropin releasing factor or stress- and anxiety-related disorders, including stress-induced depression and headache, abdominal bowel syndrome, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug and alcohol 30 withdrawal symptoms, drug addiction, and fertility problems.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with

- 36 -

the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., "Role of Bisphosphonates in Metabolic Bone Diseases" *Trends in Endocrinol. Metab.*, 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

In the case of alendronate daily oral dosage levels of 0.1 mg to 50 mg are combined for effective osteoporosis therapy with 0.01 mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention.

Osteoporosis and other bone disorders may also be treated with compounds of this invention in combination with calcitonin, estrogens, raloxifene and calcium supplements such as calcium citrate.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltestosterone, fluoxymesterone and stanozolol.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

5 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch.

10 Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

15 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents,

20 and sweetening, flavoring, and perfuming agents.

25 Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating

30 the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

- 38 -

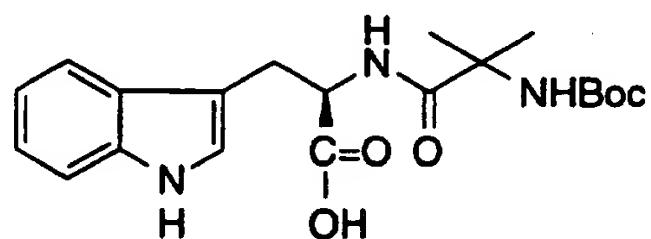
Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

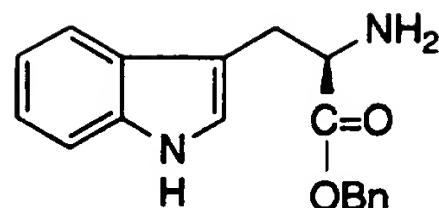
15 The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

INTERMEDIATE 1



- 39 -

Step A:

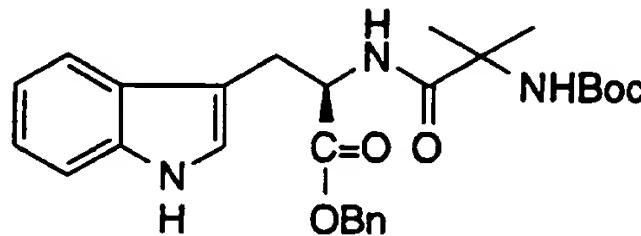


To a solution of the commercially available N-t-BOC-D-tryptophan (25.0 g, 82.2 mmol), benzyl alcohol (10.2 mL, 98.6 mmol), 5 and DMAP (100 mg) in dichloromethane (200 mL) at 0°C, was added EDC (17.4 g, 90.4 mmol) in several portions over one hour period. The reaction mixture was stirred at room temperature for six hours and was poured into water (200 mL), and the organic layer was separated. The organic solution was washed with a mixture of brine and 3 N 10 hydrochloric acid, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which solidified upon standing.

To a solution of this oil in 30 mL of dichloromethane was added 20 mL of TFA and stirred for 1h. The reaction mixture was concentrated, neutralized carefully with saturated aqueous sodium 15 bicarbonate solution, and extracted with dichloromethane (2X100 mL). The combined organic solution were washed with brine (100 mL), passed through a short column of silica gel eluting with 5-10% methanol in dichloromethane to give 23.2 g of the amine as an oil after evaporation.

20

Step B:



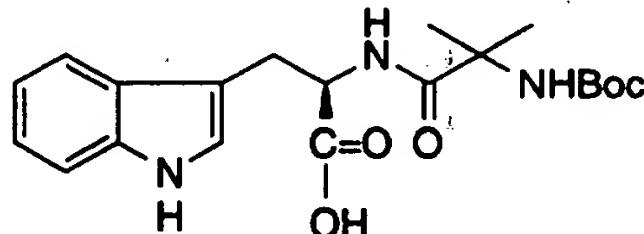
To a solution of the above product, HOBT (10.6 g, 78.8 mmol), N-BOC- α -methyl alanine (19 g, 94.5 mmol) in 200 mL of 25 dichloromethane, was added EDC (19.5 g, 0.102 mol) in several portions at 0°C. After 5 minutes, the clear reaction mixture became

- 40 -

milky. After stirring at room temperature overnight, the reaction mixture was poured into 200 mL of water and the organic layer was separated. The organic solution was washed with brine, brine and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which was purified by flash chromatography eluting with 10-40% ethyl acetate in hexane to give the desired material (28.7 g).

5 ^1H NMR (CDCl₃, 200 MHz) δ 8.48 (br.s, 1H), 7.54 (br.d, 1H), 7.38-7.23 (m, 3H), 7.19 (br.d, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (br.s, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

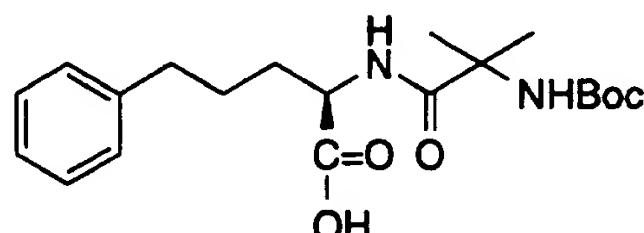
Step C:



10 A solution of the material from Step A (28.7g) in 200 mL of ethanol was stirred at RT under a H₂ balloon for 20 minutes in the presence of 10% palladium on carbon (2 g). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a slightly pink foam (23.3 g).

15 ^1H NMR (CDCl₃, 200 MHz) δ 8.60 (br.s, 1H), 7.55 (d, 1H), 7.26-6.90 (m, 3H), 6.88 (br.d, 1H), 4.80 (m, 1H), 3.32 (2 dd, 2H), 1.37 (s, 3H), 1.35 (s, 12H).

INTERMEDIATE 2



20 **Step A:** (DL)-N-acetyl-2-amino-5-phenylpentanoic acid
 To a solution of sodium (2.3 g, 0.1 mol) in ethanol (60 mL) under nitrogen at room temperature, was added diethyl

- 41 -

acetamidomalonate. The mixture was stirred at room temperature for one hour, and then 1-bromo-3-phenylpropane was added dropwisely. After the addition, the mixture was stirred at room temperature for two hours, then refluxed overnight. It was cooled to room temperature and 5 partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate in water and dried over MgSO₄ and evaporated to give an intermediate (32.5 g, 97%).
10 ¹H NMR (CDCl₃, 400MHz) 7.26-7.10 (m, 5 H); 6.75 (br. s, 1 H); 4.19 (q, J=7 Hz, 4 H); 2.58 (t, J=7.9 Hz, 2 H); 2.39-2.35 (m, 2 H); 2.00 (s, 3 H); 1.43-1.39 (m, 2 H); 1.20 (t, J=7 Hz, 6 H).

The product above was suspended in 190 mL of 2.5 N NaOH in water and refluxed for two hours. The mixture was cooled to 0°C, and it was carefully neutralized with 6 N HCl to pH=2. The 15 precipitate was collected through a glass sinter funnel and washed with small amount of cold water and air dried. The solid was then suspended in 300 mL of water and refluxed for four hours. The solution was cooled and acidified to pH=1 and the solid was collected by filtration (15.3 g, 67%).
20 ¹H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step B: (D)-N-acetyl-2-amino-5-phenylpentanoic acid
25 The racemic intermediate from last step (10 g, 42.5 mmol) and CoCl₃-6H₂O was dissolved in 21 ml of 2 N KOH and 200 mL of water at 40°C, and the pH of the solution was adjusted to 8 by addition of the several drops of 2 N KOH. The acylase I (Aspergillus sp, 0.5 u/mg, from Sigma; 0.9 g) was added with vigorous stirring. The 30 reaction mixture was stirred for one day at 40°C and the pH was kept at 8 by addition of a few drops of KOH. The solid formed was filtered. The filtrate was acidified by 3 N HCl to pH=2, and was extracted by ethyl acetate (200 mLX4). The organic extracts were combined and evaporated to give a white solid (4.64 g, 46%)

- 42 -

^1H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

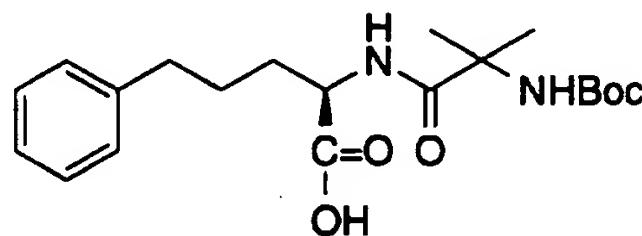
5 **Step C:** (D)-N-t-Boc-2-amino-5-phenylpentanoic acid

The intermediate from step B (4.2 g, 17.8 mmol) was suspended in 2 N HCl (100 mL) and refluxed for two hours. The reaction mixture was evaporated *in vacuo* to remove water and hydrochloric acid to yield a white solid.

10 To a solution of the solid in 50 mL of water, was added 3 N NaOH until the pH=11, then di-t-butyl dicarbonate (4.66 g, 21.4 mmol) was added with vigorous stirring. After four hours, the reaction mixture was acidified to pH=2 with 3 N HCl and it was extracted with ethyl acetate (100 mL×3). The organic extracts were combined and 15 evaporated to give a white solid (6.56 g, crude) which was used without purification.

^1H NMR (CD₃OD, 400MHz) 7.26-7.12 (m, 5 H); 4.11-4.08 (m, 1 H); 2.65-2.60 (m, 2 H); 1.83-1.62 (m, 4 H); 1.43 (s, 9 H).

20 **Step D:**

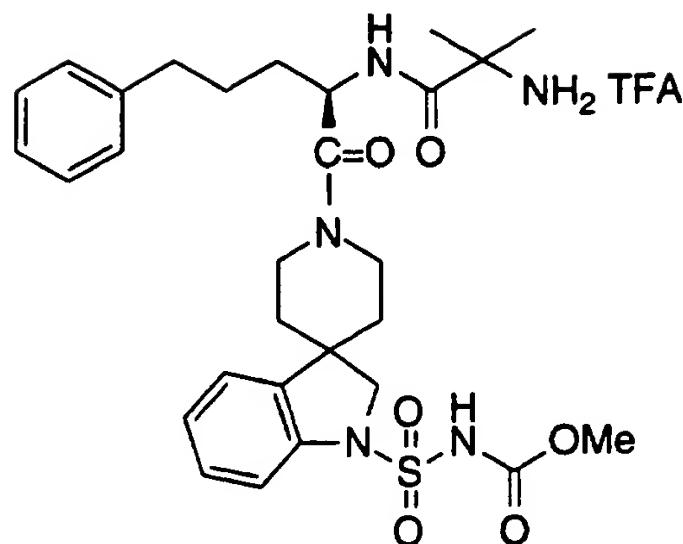


Following the procedures from the preparation of Intermediate 1 using (D)-N-t-Boc-2-amino-5-phenylpentanoic acid in the place of N-t-BOC-D-tryptophan gave Intermediate 2.

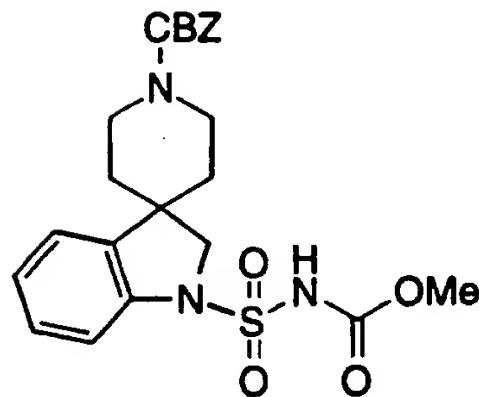
25 ^1H NMR (CDCl₃, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

- 43 -

EXAMPLE 1



Step A:



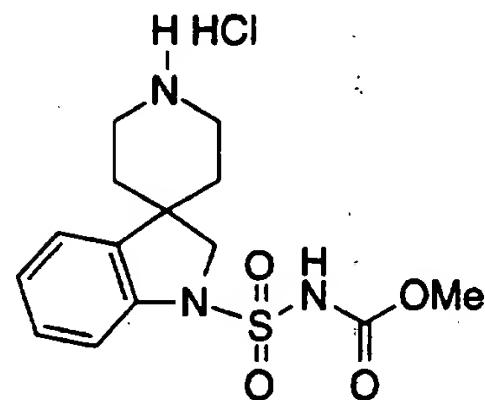
5

To a round bottom flask equipped with a magnetic bar were added to the CBZ protected spiroindoline 13 (H. Ong *et al* *J. Med. Chem.* 1983, 23, 981-986) (12.9 g, 40.0 mmol), diisopropyl ethyl amine (5.17 g, 40.0 mmol) and methylene chloride (120 ml). Once the starting material was dissolved, the mixture was cooled to 0°C and then of methyl (chlorosulfonyl) carbamate (8.33 g) was added slowly. Stirring was kept at 0°C for 30 minutes, and then at room temperature for another 30 minutes. The reaction mixture was diluted with 150 ml methylene chloride and washed with brine, and then the aqueous layer was further extracted with methylene chloride (X1). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (silica gel; hexane-ethyl acetate as eluent) provided the desired product as white solid (15.3 g).

- 44 -

¹H NMR (CDCl₃, 400 MHz) δ 7.70 (br.s, 1 H), 7.70-7.06 (m, 4 H), 5.15 (s, 2 H), 4.24 (s, 2 H), 3.66 (s, 3H), 2.93 (br.s, 2 H), 1.82-1.70 (m, 4 H). FAB-MS calc. for C₂₂H₂₅N₃O₆S: 459; Found: 460 (M+1).

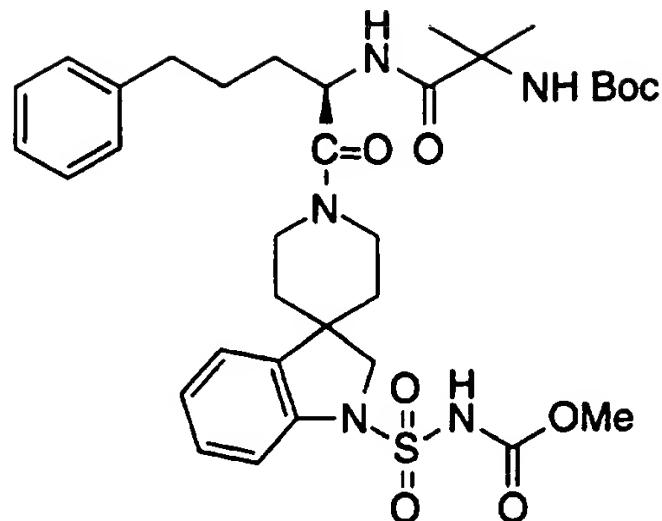
5 Step B:



To a solution of the compound obtained (13.0 g, 28.3 mmol) from Step 1 in methanol-ethyl acetate solution (300 ml, 5:1) were added concentrated hydrochloride (2.36 ml, 28.3 mmol) and 20% Pd(OH)₂/C (2.6 g). Under a hydrogen balloon, the reaction mixture was stirred at room temperature for 4 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the desired product as white solid (7.58 g).

Step C:

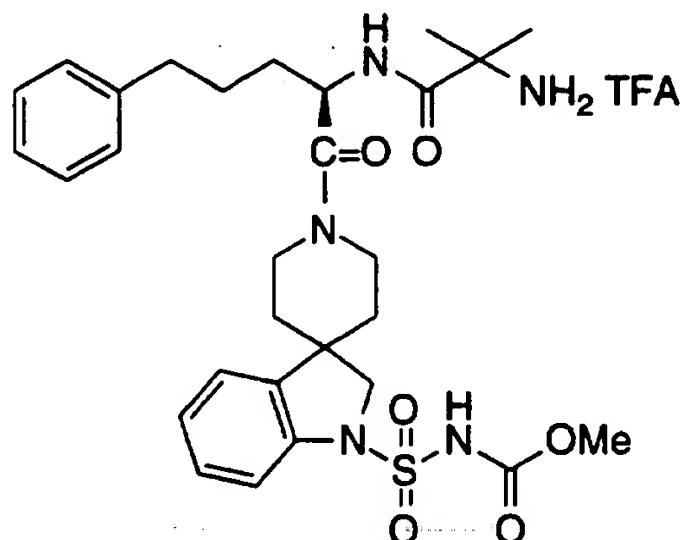
- 45 -



To a solution of the compound obtained from step 2 (250.0 mg, 0.69 mmol), Intermediate 2 (261.0 mg, 0.69 mmol), NMM (140.0 ml, 1.38 mmol) and HOBT (93.0 mg, 0.69 mmol) in methylene chloride (10 ml) was slowly added EDC (198.0 mg, 1.04 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction was diluted with methylene chloride and washed with 2 N HCl aqueous solution. The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was brought to flash column chromatography (silica gel, hexane-ethyl acetate-acetic acid as eluent) to give the desired product as white solid (137.7 mg).

FAB-MS calc. for C₃₄H₄₇N₅O₈: 685 found: 686 (M+1).

15 Step D:



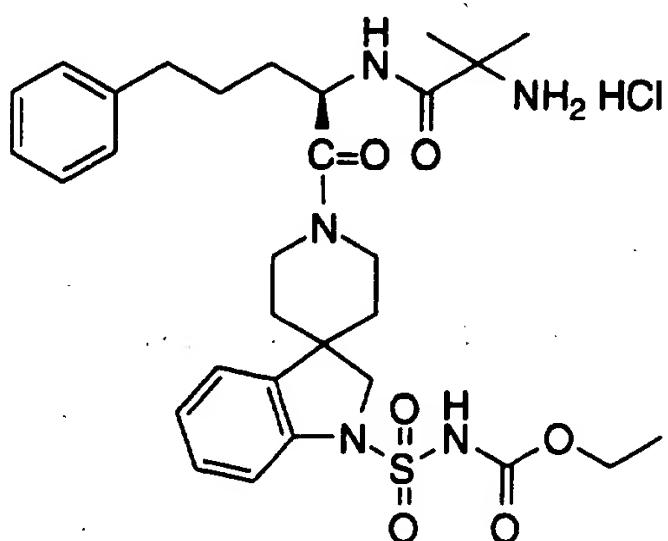
- 46 -

The compound (250.0 mg) obtained from step 3 was dissolved in 2 ml methylene chloride, followed by addition of 8 ml trifluoroacetic acid. The reaction mixture was allowed to stir at room temperature for 4 hours, and then 10 ml toluene was added to the reaction flask. The reaction mixture was concentrated in vacuo to provide 235.0 mg of the desired product.

¹HNMR (CDCl₃, 400 MHz) δ 7.29-7.01 (m, 9H); 4.52-4.44 (br. m, 1 H); 4.26 (dd 2H); 3.95-3.82 (m); 3.63 (s, 3H); 3.30-3.18 (br. dd), 2.88-2.75 (m); 2.75-2.60 (m); 2.02-1.94 (dt, 1H); 1.80-1.65 (m), 1.62 (s); 1.60 (s). FAB-MS calc. for C₂₉H₃₉N₅O₆: 585 found: 586 (M+1).

Additional growth hormone secretagogues shown in Tables I were prepared according to the established procedure shown in Examples 1 using the appropriate alkyl-(chlorosulfonyl)carbamate

15 instead of methyl-(chlorosulfonyl)carbamate, which was prepared from the reaction of an alcohol with chlorosulfonyl isocyanate (Burgess *et al*, Organic Syntheses vol. VI, 788), to react with the intermediate in example 1 step A. For example, the use of ethanol instead of methanol led to the following compound.



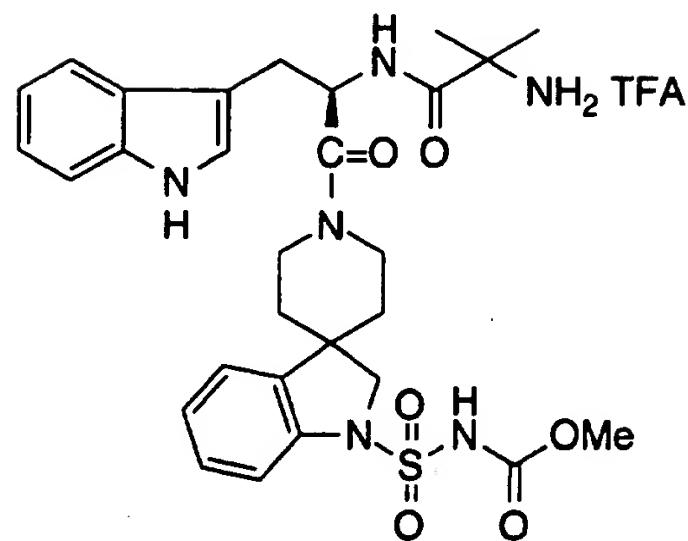
20

¹HNMR (CDCl₃, 400 MHz) δ 7.29-7.01 (m, 9H); 4.50-4.47 (m 1 H), 4.25 (appeared as d, 2 H); 4.06 (q, J=7.1 Hz, 2 H); 3.94-3.85 (br. m, 1 H), 3.29-3.20 (m, 2 H), 2.89-2.60 (m, 3 H), 2.05-1.95 (m, 1 H), 1.80-1.65 (m), 1.62 (s), 1.60 (s), 1.14 (t, J=7.1 Hz, 3 H).

25 FAB-MS calc. for C₃₀H₄₁N₅O₆: 599 found: 600 (M+1).

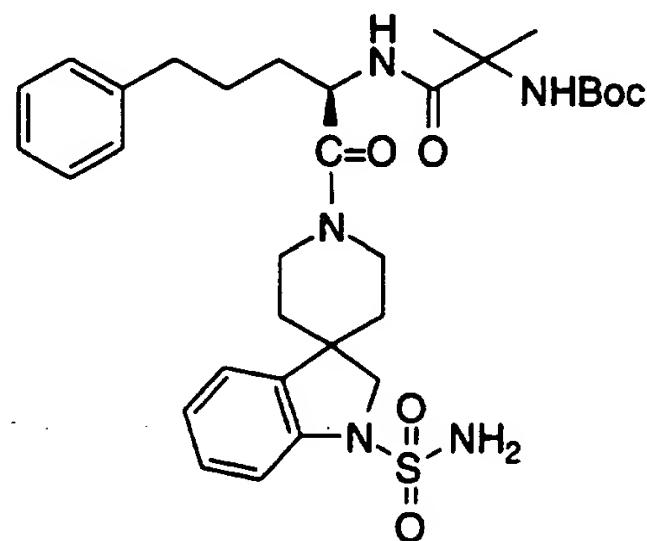
- 47 -

EXAMPLE 2



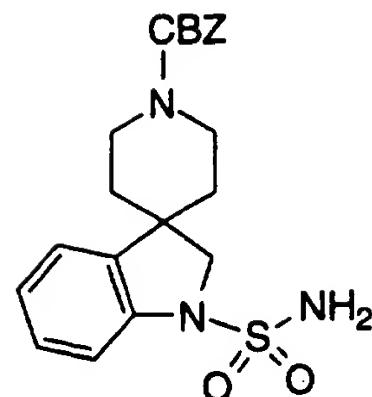
The compound was prepared by the procedure described in
5 Example 1, except that Intermediate 1 was used instead of Intermediate
2. FAB-MS calc. for $C_{29}H_{36}N_6O_6S$:596 found: 597(M+1).

INTERMEDIATE 3



10 Step A:

- 48 -



To a round bottom flask charged with of chlorosulfonyl isocyanate (13.3 g, 93.6 mmol), was added formic acid (4.2 g, 93.6 mmol) dropwise while the temperature was kept below 5°C. The reaction mixture was allowed to stir at room temperature until gas evolution ceased. To this resulting sulfamoyl chloride mixture was slowly added a solution of the spiroindoline (23.4 g, 72 mmol) and diisopropylethyl amine (10.2 g, 79.2 mmol) in THF (250 ml). The reaction mixture was allowed to stir at room temperature overnight, and then was poured to cold 2 N HCl solution and extracted with methylene chloride three times. Organic layers were combined, dried and concentrated to provide a yellow oil, which was brought to flash column chromatography (silica gel, 40% ethyl acetate in hexane) to provide 20.7 g of the desired product as white solid.

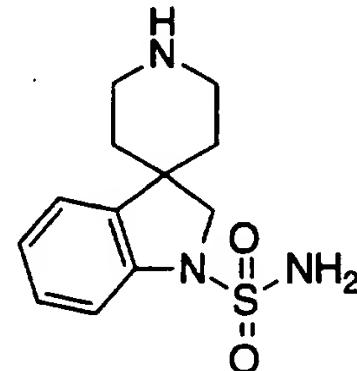
5

10

15

¹HNMR (CDCl₃, 400 MHz) δ 7.41-7.02 (m, 9 H), 5.14 (s, 2 H), 4.81 (s, 2 H), 4.19 (br.s, 2 H), 3.81 (s, 2 H), 2.94 (br.s, 2 H), 1.83-1.64 (m, 4 H). FAB-MS calc. for C₂₀H₂₃N₃O₄S: 401, Found: 402 (M+1).

Step B:



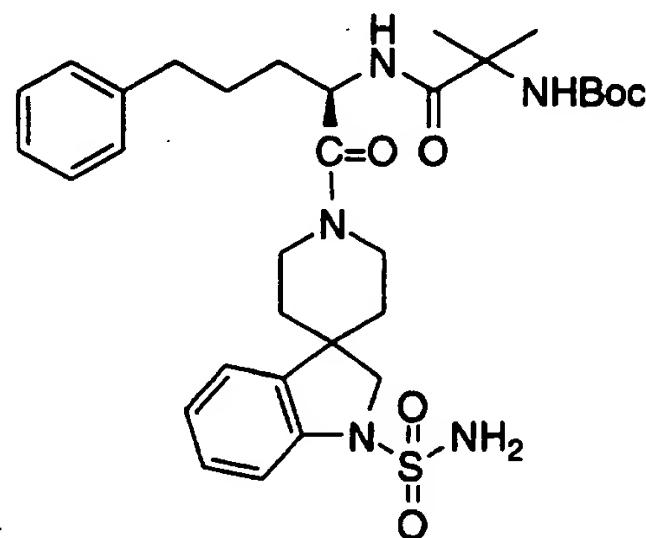
- 49 -

A suspension of 10% palladium on carbon (100 mg) and the intermediate from the previous step (838 mg, 2.1 mmol) in ethanol (20 mL) was stirred under a hydrogen atmosphere overnight at room temperature. The reaction mixture was then filtered through celite and evaporated to give the product (568 mg, 100%).

5 ^1H NMR (CD₃OD, 400 MHz): δ 7.37 (d, $J=7.8$ Hz, 1 H); 7.21-7.15 (m, 2 H), 7.01 (dt, $J=7.2$, 1.0 Hz, 1 H); 3.83 (s, 2 H); 3.06 (br. td, 2H), 2.77 (dt, $J=2.8$, 13 Hz, 2 H); 1.86 (dt, $J=4.2$, 13.5 Hz, 2 H); 1.68 (br.d, $J=13.5$ Hz, 2 H). FAB-MS calc. for C₁₂H₁₇N₃O₂S: 267; Found 268

10 (M+H).

Step C:



To a solution of the intermediate prepared in the previous step (544 mg, 2.03 mmol), Intermediate 2 (770 mg, 2.03 mmol), and HOBT (275 mg, 2.03 mmol) in dichloromethane at 0°C was added EDC (1.5 eq.). The reaction mixture was stirred overnight during which time the temperature was warmed to ambient temperature. The solution was washed with 3 N hydrochloric acid, saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 70% ethyl acetate in hexane gave the product (1.05 g, 82%).

15

20

^1H NMR (CD₃OD, 400 MHz): δ 7.64 (dd, $J=8.5$, 11.8 Hz, 1 H), 7.38 (d, $J=7.5$ Hz, 1 H); 7.26-6.92 (m, 7 H); 4.95-4.82 (m, 1H); 4.46 (br. d,

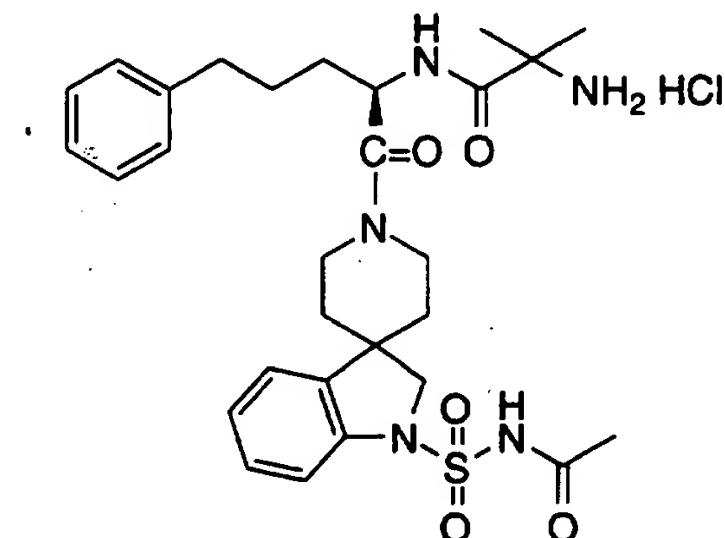
- 50 -

$J=13.3$ Hz, 1 H); 3.90-3.80 (dd, 2 H); 3.28-3.12 (m, 1 H); 2.88-2.80 (m, 1 H); 2.70-2.64 (m, 2 H); 2.00-1.52 (m); 1.42 (s); 1.38 (s)

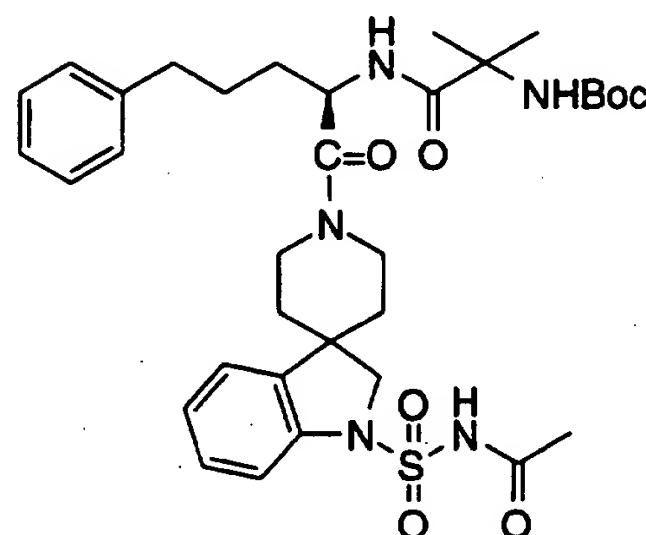
FAB-MS calc. for C₃₂H₄₅N₅O₆S: 627 found: 628 (M+1).

5

EXAMPLE 3



Step A:



10 To a stirred solution of the intermediate from previous step
(250 mg, 0.398 mmol), NMM (0.13 mL, 1.2 mmol), and DMAP (10
mg) in dichloromethane (10 mL) at 0°C was added acetic anhydride
(0.075 mL, 0.8 mmol). The reaction mixture was stirred at 0°C for 1
h, and TLC (silica gel, developing with 80% ethyl acetate in hexane)
15 indicated the reaction was over. The reaction mixture was diluted with
ethyl acetate (20 mL) and washed with 3 N hydrochloric acid and brine;

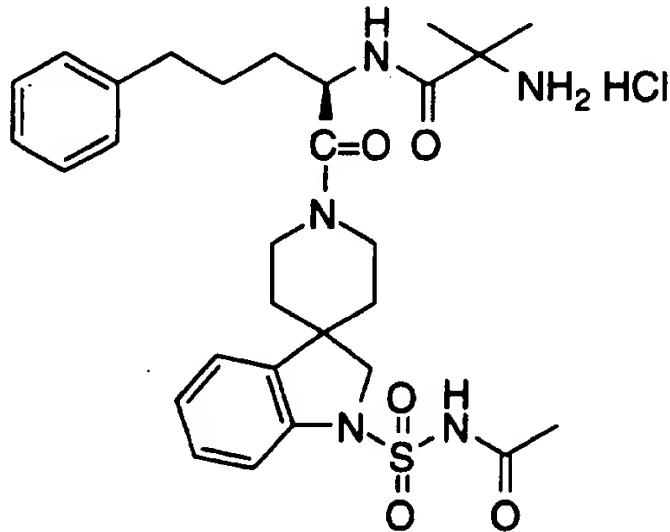
- 51 -

dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 80% ethyl acetate in hexane gave the product (216 mg, 82%).

5 ^1H NMR (CDCl₃, 400 MHz) δ 7.29-7.01 (m, 9H); 4.52-4.44 (br. m, 1 H); 4.26 (dd 2H); 3.95-3.82 (m); 3.63 (s, 3H); 3.30-3.18 (br. dd), 2.88-2.75 (m); 2.75-2.60 (m); 2.02-1.94 (dt, 1H); 1.80-1.65 (m), 1.62 (s); 1.60 (s). FAB-MS calc. for C₃₄H₄₇N₅O₇S: 669 found: 670 (M+1)

Step B:

10



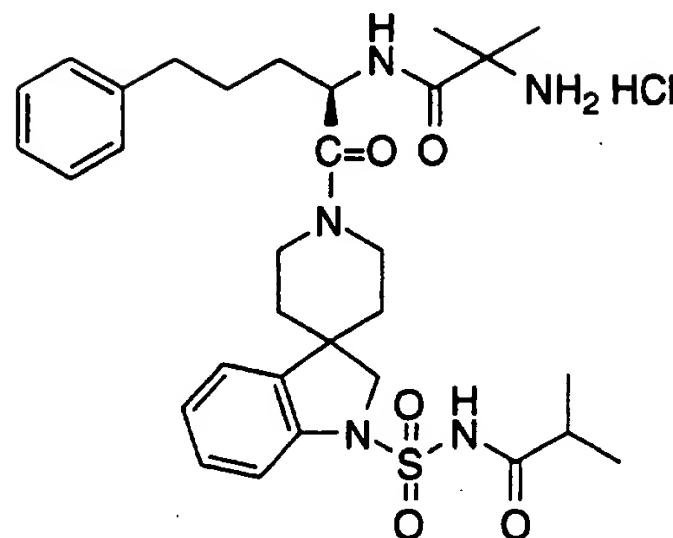
A solution of the compound from Step A (196 mg) in ethyl acetate (5 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes. The solution was then concentrated to remove ethyl acetate. The residue was then redissolved in dichloromethane and hexane followed by evaporation *in vacuo* to afford the product as a solid (170 mg).

15 FAB-MS calc. for C₂₉H₃₉N₅O₅S: 428 ; Found: 429 (M+H).

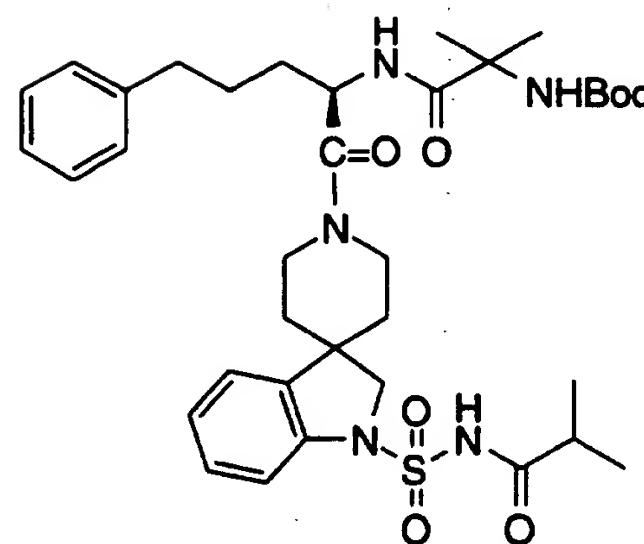
20 ^1H NMR (CD₃OD, 400 MHz) δ 7.28-7.01 (m, 9 H); 4.50-4.46 (br, m, 1 H); 4.27 (appears as d, 2 H); 3.94-3.84 (br. dd, 1H); 3.28-3.16 (b m 1 H); 2.86-2.75 (m, 1H); 2.70-2.60 (m, 2H); 1.92 (s, 3 H); 1.80-1.50 (m); 1.61 (s). FAB-MS calc. for C₂₉H₃₉N₅O₆S: 585 found: 586 (M+1).

- 52 -

EXAMPLE 4



Step A:



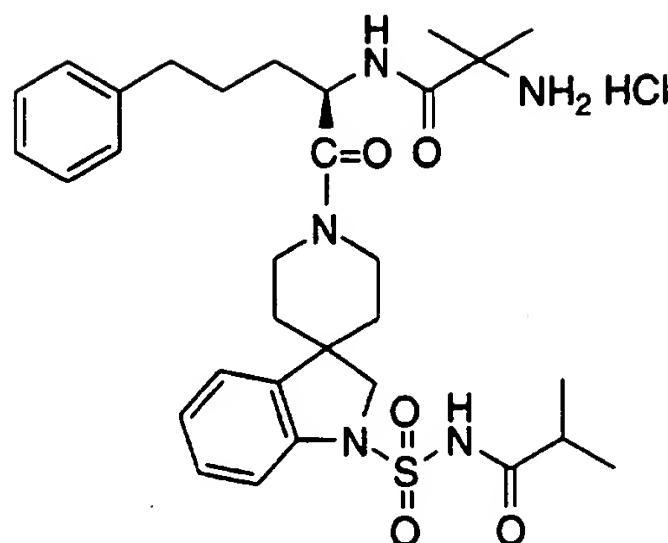
5 To a stirred solution of the intermediate from step (250 mg, 0.398 mmol), NMM (0.13 mL, 1.2 mmol), and DMAP (10 mg) in dichloromethane (10 mL) at 0°C was added isobutyryl chloride (0.063 mL, 0.6 mmol). The reaction mixture was stirred at 0°C for 1 h, and TLC (silica gel, developing with 80% ethyl acetate in hexane) indicated the reaction was over. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 3 N hydrochloric acid and brine; dried over anhydrous magnesium sulfate; then filtered and concentrated.

10 Purification by MPLC eluting with 60% ethyl acetate in hexane gave the product (261.9 mg, 94%).

15 FAB-MS calc. for C₃₆H₅₁N₅O₇S: 697 found: 698 (M+1).

- 53 -

Step B:



Prepared by the procedure described in Example 1, Step B from the intermediate from the previous step (241 mg, 0.34 mmol) and

5 HCl gas at 0°C in ethyl acetate (3 mL) for 20 minutes. Product: 200 mg.

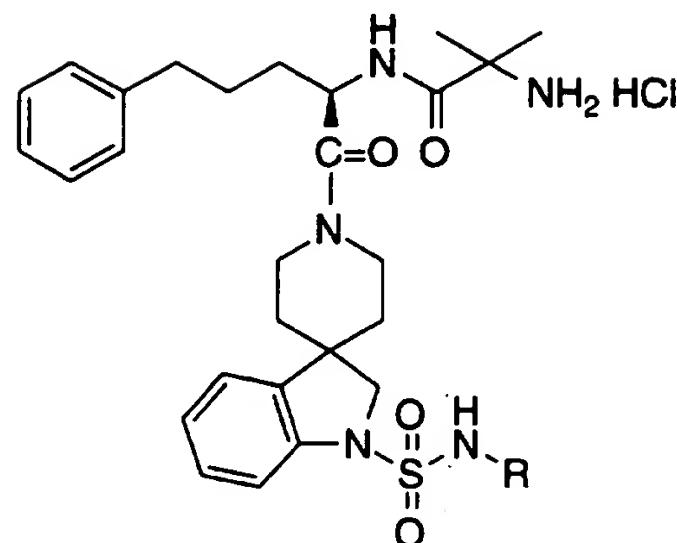
10 ^1H NMR (CD₃OD, 400 MHz) δ 7.29-7.01 (m, 9 H); 4.52-4.46 (br, m, 1 H); 4.30 (apparent d, 2H); 3.95-3.84 (m 1 H); 3.32-3.18 (br, dd, 1H); 2.86-2.75 (m, 1H); 2.70-2.60 (m, 2H); 2.42-2.35 (m, 1 H); 1.80-1.50 (m); 1.61 (s); 0.93 (d, 6H). FAB-MS calc. for C₃₁H₄₃N₅O₅S 597 ; Found: 598 (M+H)

The additional growth hormone secretagogues shown in Tables I were prepared according to the established procedure shown in

15 Examples 3 and 4 using the appropriate anhydride or acyl chloride instead of acetic anhydride or isobutyryl chloride to react with the Intermediate 3. The characterization included FAB-MS and NMR studies. Similarly, other analogs can be prepared the same way.

- 54 -

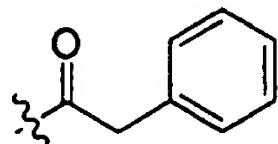
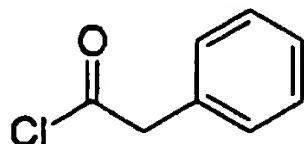
TABLE I



Example	Acyl chloride	R	molecular formula FAB-MS (M+1)
5			C ₃₂ H ₄₅ N ₅ O ₅ S 612
6			C ₃₄ H ₄₁ N ₅ O ₅ S 632
7			C ₃₄ H ₄₀ N ₅ O ₅ SCl 666
8			C ₃₅ H ₄₃ N ₅ O ₆ S 662
9			C ₄₁ H ₄₇ N ₅ O ₅ S 722

- 55 -

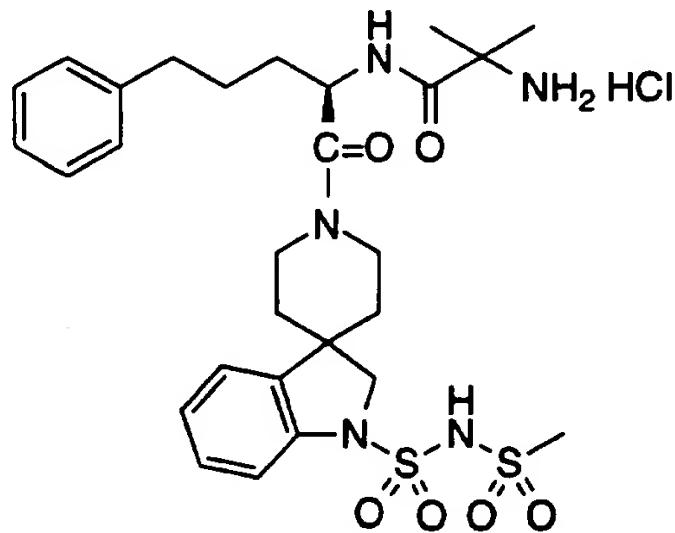
10



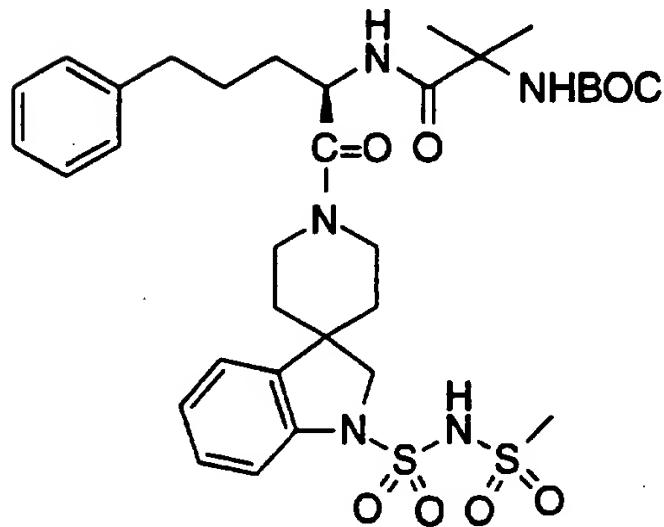
C₃₅H₄₃N₅O₅S
646

EXAMPLE 11

5



Step A:



To a stirred solution of the Intermediate 3 (125.6 mg, 0.20 mmol), DMAP (12.2 mg, 0.10 mmol) and diisopropylethylamine (69.0 ml, 0.4 mmol) in methylene chloride (2 ml) was added methanesulfonyl chloride (45.8 mg, 0.4 mmol), and then the reaction mixture was kept stirring at room temperature overnight. The reaction mixture was 10 diluted with methylene chloride and washed with 2 N HCl solution once.

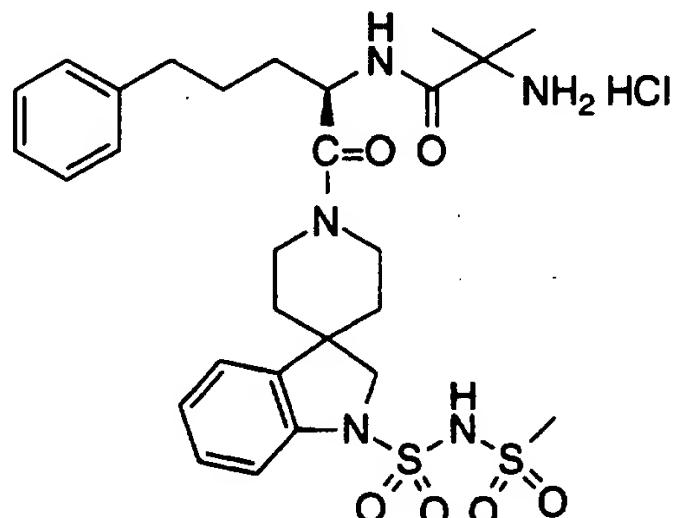
- 56 -

The organic layer was dried, concentrated and purified silica gel column (1% HOAc:10% MeOH in EtOAc as eluent) to give 66.8 mg of the desired product.

FAB-MS calc. for C₃₃H₄₇N₅O₈S₂: 705, Found: 706 (M+1).

5

Step B:



The compound obtained from step 4 was dissolved in ethyl acetate and hydrogen chloride gas was bubbled into the mixture until 10 saturation occurred. The reaction solution was allowed to stir at room temperature for 30 minutes, and then small amounts of hexane and methylene were added. This mixture was brought to vacuo to give the desired product as a solid.

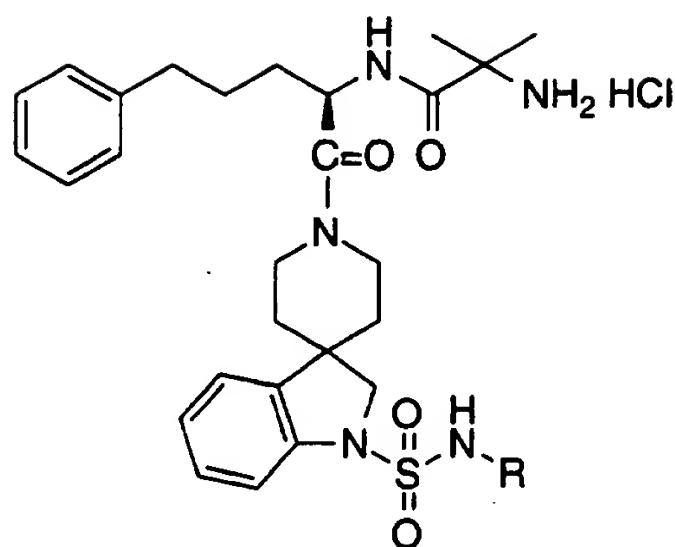
FAB-MS calc. for C₂₈H₃₉N₅O₆S₂: 605, Found: 606.

15

The additional growth hormone secretagogues shown in Table II were prepared according to the established procedure shown in Example 5 using the appropriate sulfonyl chloride instead of methanesulfonyl chloride to react with the Intermediate 3. The 20 characterization included FAB-MS and NMR studies. Similarly, other analogs can be prepared the same way.

- 57 -

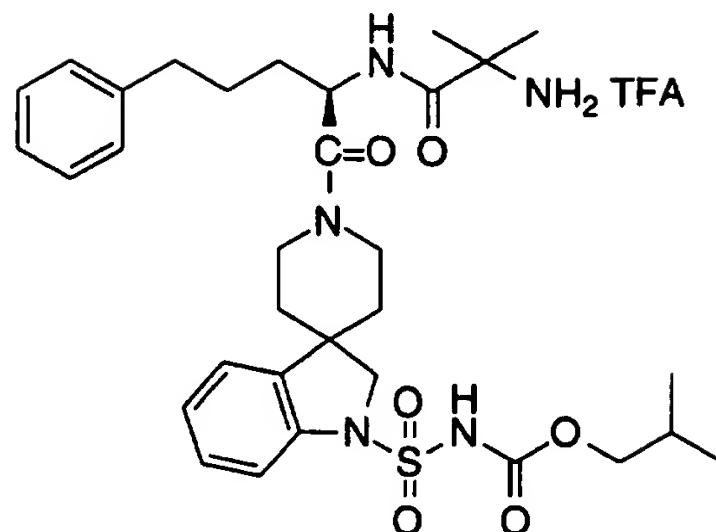
TABLE II



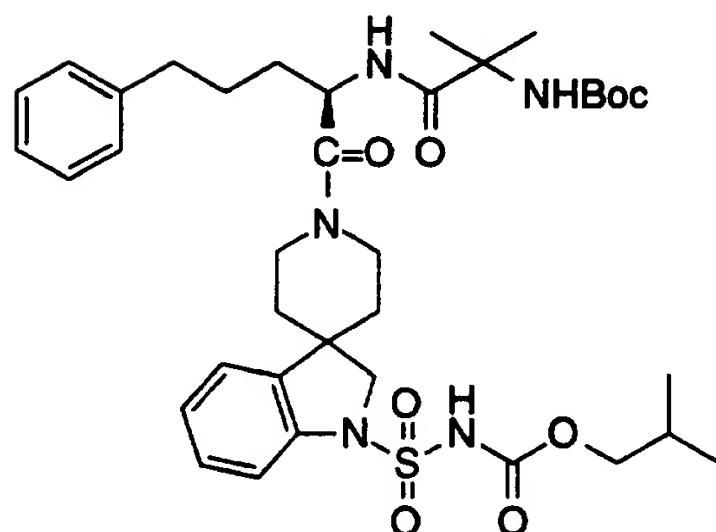
Example	sulfonyl chloride	R	molecular formula FAB-MS (M+1)
12			C ₃₂ H ₄₂ N ₆ O ₆ S 639
13			C ₃₂ H ₄₂ N ₆ O ₇ S 698

- 58 -

EXAMPLE 4



Step A:

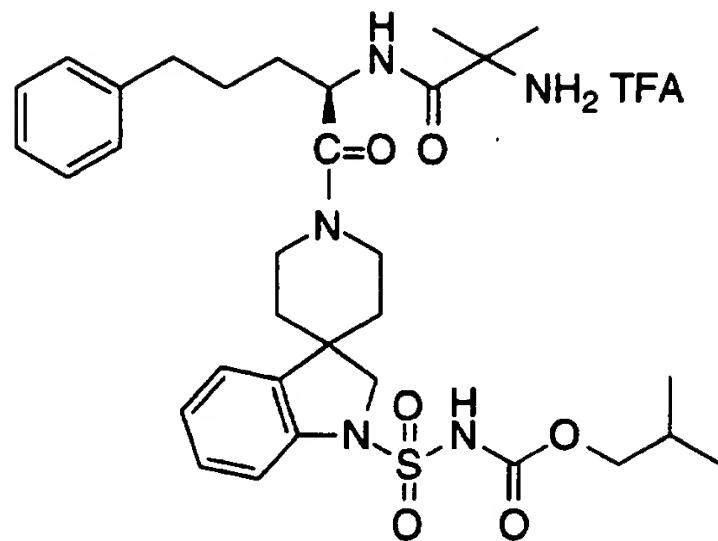


5 To a stirred solution of the Intermediate 3 (209 mg, 0.32 mmol), DMAP (12.2 mg, 0.10 mmol) and diisopropylethylamine (83 mg, 0.64 mmol) in methylene chloride (8 ml) was added isobutyl chloroformate (87 mg, 0.64 mmol), and then the reaction mixture was kept stirring at room temperature overnight. The reaction mixture was 10 diluted with methylene chloride and washed with 2 N HCl solution once. The organic layer was dried, concentrated and purified on silica gel column (1% HOAc:10% MeOH in EtOAc as eluent) to give 173 mg of the desired product (74%).

FAB-MS calc. for C₃₇H₅₃N₅O₈S: 727, Found: 728 (M+1).

- 59 -

Step B:



5 The compound obtained from step 4 was dissolved in ethyl acetate and hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction solution was allowed to stir at room temperature for 30 minutes, and then small amounts of hexane and methylene were added. This mixture was brought *to vacuo* to give the desired product as a solid.

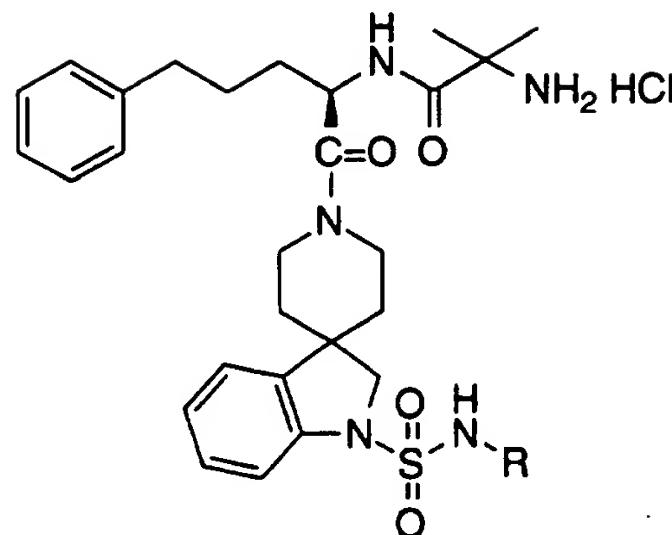
10 FAB-MS calc. for C₃₂H₄₅N₅O₆S: 627, Found: 628 (M+1).

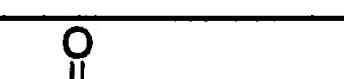
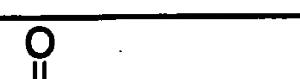
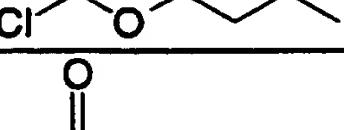
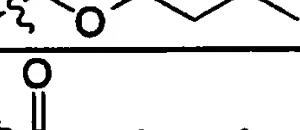
15

The additional growth hormone secretagogues shown in Table III were prepared according to the established procedure shown in Example 14 using the appropriate chloroformate instead of isobutyl chloroformate to react with the Intermediate 3. The characterization included FAB-MS and NMR studies. Similarly, other analogs can be prepared the same way.

- 60 -

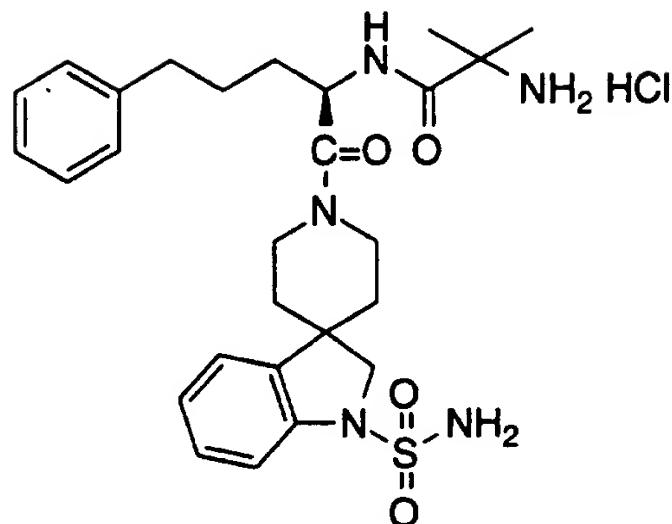
TABLE III



Example	chloroformate	R	molecular formula FAB-MS (M+1)
15			C ₃₂ H ₄₅ N ₅ O ₆ S 628
16			C ₃₅ H ₄₃ N ₅ O ₆ S 662

- 61 -

EXAMPLE 17



To a stirred solution of the intermediate 3 (200 mg) in ethyl acetate (3 mL) at 0°C, was bubbled HCl gas until it was saturated.

5 The mixture was stirred for 20 minutes, and evaporated to dryness. The solid was washed with small ethyl acetate, dried under vacuum to give the product (174 mg).

1 ¹HNMR (DMSO-D₆, 400 MHz) δ 8.47 (dd, J=8.4, 11.7 Hz, 1 H), 8.24 (br. s, 3 H); 7.33-6.97 (m, 9 H); 4.80-4.76 (br. m, 1 H), 4.35 (br. d, 10 J=12.8 Hz, 1 H), 3.85 (br. d, 1 H), 3.21-3.12 (br. m, 1 H), 2.80-2.69 (br. m, 1 H), 2.65-2.50 (m, 2 H), 1.75-1.55 (m, 8 H); 1.49,1.48 (s, 6 H) FAB-MS calc. for C₂₇H₃₇N₅O₄S: 527, Found: 528 (M+1).

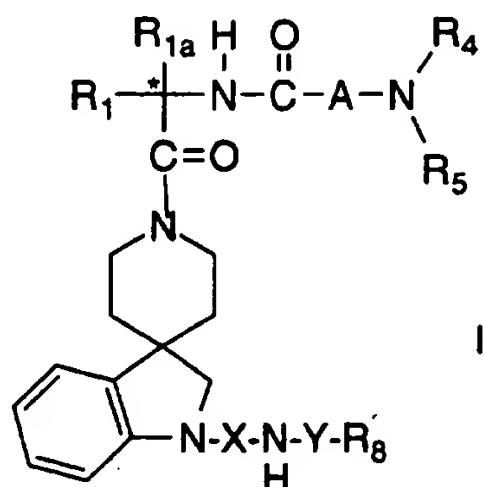
- 62 -

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

- 63 -

WHAT IS CLAIMED IS:

1. A compound of the formula I:



5 wherein:

R₁ is selected from the group consisting of:
 C₁-C₁₀ alkyl-, aryl-, aryl(C₁-C₆ alkyl)-,
 heteroaryl-, heteroaryl(C₁-C₆ alkyl)-,
 10 (C₃-C₇ cycloalkyl)-(C₁-C₆ alkyl) -,
 (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 aryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 heteroaryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and
 (C₃-C₇ cycloalkyl)-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl) -,
 15 wherein K is -O-, -S(O)_m-, -N(R₂)C(O)-, -C(O)N(R₂)-, -OC(O)-,
 -C(O)O-, -CR₂=CR₂- or -C≡C-,
 wherein R₂ and the alkyl groups are optionally further substituted with
 20 1 to 9 halo, -S(O)_mR_{2a}, 1 to 3 of -OR_{2a}, or -C(O)OR_{2a}, and wherein
 aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl,
 thiophenyl, furanyl, benzothiophenyl, benzofuranyl, pyridinyl,
 quinolinyl, triazolyl, imidazolyl, thiazolyl, and benzimidazolyl, wherein
 aryl and heteroaryl are unsubstituted or substituted with phenyl,
 phenoxy, halophenyl, 1 to 3 of -C₁-C₆ alkyl, 1 to 3 of halo, 1 to 2 of
 -OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro,
 25 -N(R₂)(R₂), -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂),
 -SO₂N(R₂)(R₂), -N(R₂)SO₂-aryl, or -N(R₂)SO₂R₂;

- 64 -

R_{1a} is hydrogen or C₁-C₄ alkyl;

R₂ is selected from the group consisting of:

5 hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl, wherein the alkyl or the cycloalkyl is unsubstituted or substituted with hydroxyl, C₁-C₃ alkoxy, thioalkyl, C(O)OR_{2a}, and wherein, if two -C₁-C₆ alkyl groups are present on one atom, the groups are optionally joined to form a C₃-C₈ cyclic ring optionally including oxygen, sulfur, or NR_{2a}, the C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine;

10 or NR_{2a}, the C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine;

R_{2a} is hydrogen or C₁-C₆ alkyl;

15 R₄ and R₅ are independently selected from the group consisting of: hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl where the substituents are selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C₁-C₁₀ alkanoyloxy, 1 to 3 C₁-C₆ alkoxy, phenyl, phenoxy, 2-furyl, C₁-C₆ alkoxycarbonyl, and -S(O)_m(C₁-C₆ alkyl); or wherein R₄ and R₅ are optionally taken together to form -(CH₂)_rL_a(CH₂)_s-, wherein L_a is -C(R₂)₂-, -O-, -S(O)_m- or -N(R₂)-, wherein r and s are independently 1 to 3, and R₂ is defined above;

20 or wherein R₄ and R₅ are optionally taken together to form -(CH₂)_rL_a(CH₂)_s-, wherein L_a is -C(R₂)₂-, -O-, -S(O)_m- or -N(R₂)-, wherein r and s are independently 1 to 3, and R₂ is defined above;

25 A is:



wherein x and y are independently 0, 1, 2 or 3;

- 65 -

Z is -N(R9)- or -O-, wherein R9 is hydrogen or C₁-C₆ alkyl;

R₁₀ and R_{10a} are independently selected from the group consisting of:
hydrogen, -C₁-C₆ alkyl, trifluoromethyl, phenyl, and substituted C₁-C₆
5 alkyl wherein the substituents are selected from the group consisting of:
imidazolyl, phenyl, indolyl, naphthyl, p-hydroxyphenyl, -OR₂,
-S(O)_mR₂, -C(O)OR₂, -C₃-C₇ cycloalkyl, -N(R₂)(R₂), and
-C(O)N(R₂)(R₂);
or R₁₀ and R_{10a} are optionally independently joined to one or both of
10 R₄ and R₅ groups to form an alkylene bridge between the terminal
nitrogen and the alkyl portion of the R₁₀ or R_{10a} groups, wherein the
bridge contains 1 to 5 carbons atoms;

R₈ is hydrogen, C₁-C₁₀ alkyl, phenyl, benzyl or diphenyl methyl
15 wherein the phenyl, benzyl or diphenyl groups may be substituted by
halo, methyl or OR₂;

X is SO₂ or CO; and
Y is selected from a chemical bond, SO₂, CO, C(O)O, C(O)N(R₂), and
20 SO₂ N(R₂);
m is 0, 1, or 2; and
n is 1 or 2;

25 and pharmaceutically acceptable salts and individual diastereomers
thereof.

- 66 -

2. The compound of Claim 1 wherein:

R₁ is selected from the group consisting of:

C₁-C₁₀ alkyl, aryl(C₁-C₄ alkyl)-,

5 C₅-C₆ cycloalkyl-(C₁-C₄ alkyl)-, (C₁-C₄ alkyl)-K-C₁-C₂ alkyl-,
aryl(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-,
C₃-C₆cycloalkyl(C₀-C₂alkyl)-K-(C₁-C₂alkyl)-, wherein K is O or
S(O)_m, and the aryl is phenyl, or naphthyl and the heteroaryl is indolyl
and the aryl and heteroaryl groups are unsubstituted or substituted by
10 1 to 2 C₁-C₄ alkyl, 1 to 2 halo, OR₂, C(O)OR₂, CF₃ or S(O)_mR₂;

R₂ is selected from the group consisting of:

hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, wherein the alkyl or the
cycloalkyl is unsubstituted or substituted with hydroxyl, C₁-C₃ alkoxy,

15 thioalkyl, C(O)OR_{2a}, and, if two C₁-C₆ alkyls are present on one atom,
they are optionally joined to form a C₅-C₆ cyclic ring optionally
including the heteroatoms oxygen or NR_{2a}, the C₃-C₈ cyclic ring being
selected from the group consisting of pyrrolidine, piperidine,
piperazine, morpholine, thiomorpholine;

20

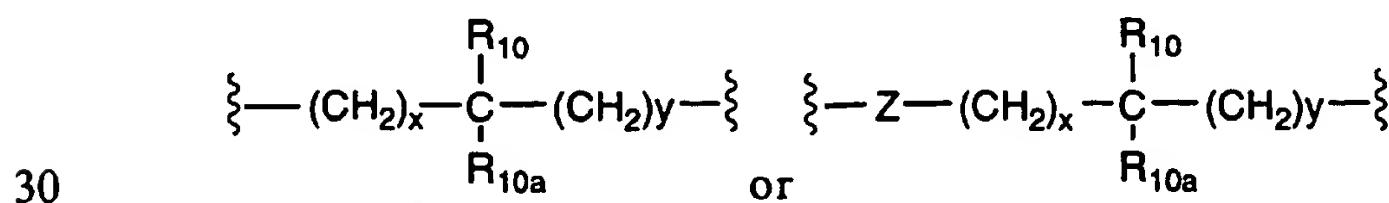
R_{2a} is hydrogen or C₁-C₄ alkyl;

R₄ and R₅ are independently selected from the group consisting of:

hydrogen, C₁-C₄ alkyl, substituted C₁-C₄ alkyl where the substituents

25 may be 1 to 2 hydroxy or S(O)_m(C₁-C₃alkyl); or wherein R₄ and R₅
may be taken together to form (CH₂)_rN(R₂)(CH₂)_s wherein r and s are
independently 1 to 3 and R₂ is defined above;

A is:



- 67 -

wherein x and y are independently 0,1 or 2;

Z is -N(R₉)- or -O-, wherein R₉ is hydrogen or C₁-C₄ alkyl;

5 R₁₀ and R_{10a} are independently selected from the group consisting of: hydrogen, C₁-C₃ alkyl; or R₁₀ and R_{10a} are optionally independently joined to one or both of the R₄ and R₅ groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R₁₀ or R_{10a} groups to form 5 or 6 membered rings containing the terminal
10 nitrogen;

X is SO₂;

Y is CO, CO₂, or SO₂;

R₈ is C₁-C₆ alkyl, phenyl or benzyl optionally substituted with halo,

15 methyl or OR₂;

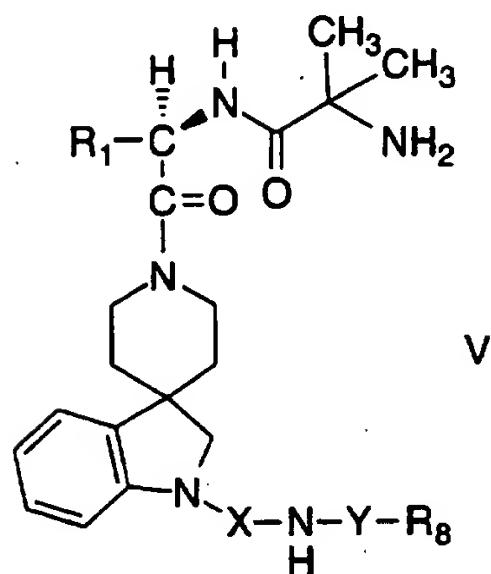
m is 0, 1, or 2; and

n is 1;

20 or their pharmaceutically acceptable salts and individual diastereomers thereof.

- 68 -

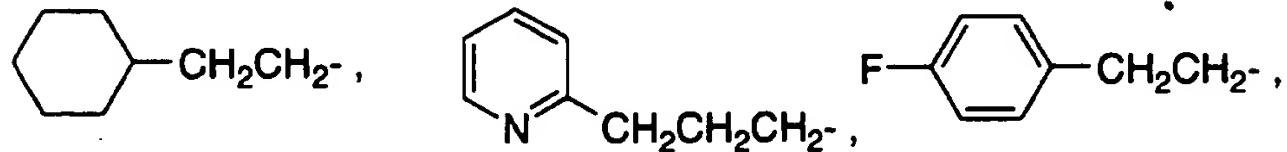
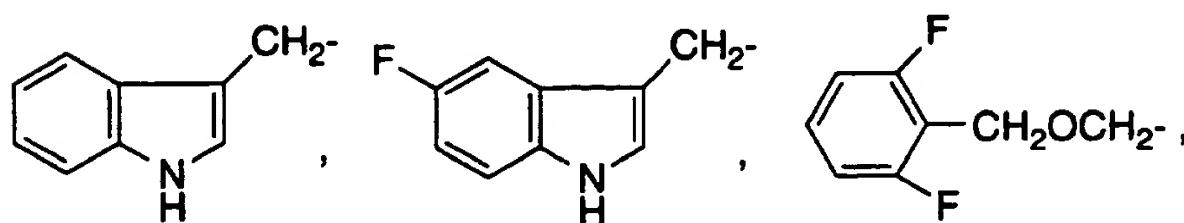
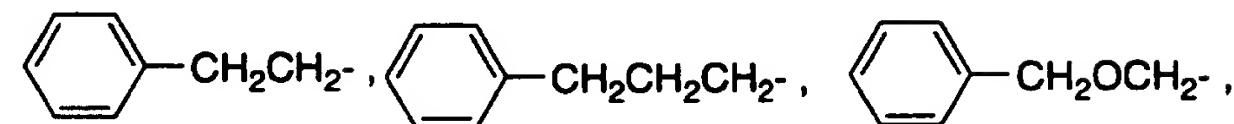
3. The compound of Claim 1 of the structural formula V:



5

wherein:

R1 is selected from the group consisting of:



and

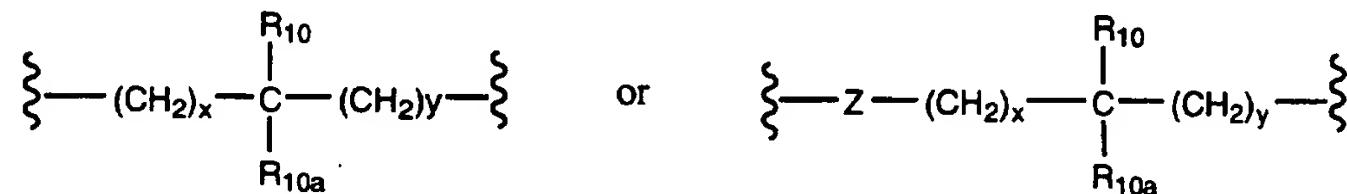
10 R2 is selected from the group consisting of:
hydrogen, C1-C4 alkyl;

- 69 -

R_4 and R_5 are independently selected from the group consisting of hydrogen, C₁-C₄ alkyl, substituted C₁-C₄ alkyl wherein the substituents are 1 to 2 hydroxy or wherein R_4 and R_5 maybe taken together to form piperazine;

5

A is



10 wherein x and y are independently 0, 1 or 2;

Z is N(R_9) or -O-, wherein R_9 is hydrogen or methyl;

15 R_{10} and R_{10a} are independently selected from the group consisting of hydrogen and C₁-C₃ alkyl; or R_{10} and R_{10a} are optionally independently joined to one or both of the R_4 and R_5 group to form a pyrrolidine or piperidine ring;

20 X is SO₂;

20

Y is CO or SO₂;

25 R_8 is hydrogen, C₁-C₄ alkyl, phenyl or benzyl optionally substituted by halo, methyl or OR₂; and

25

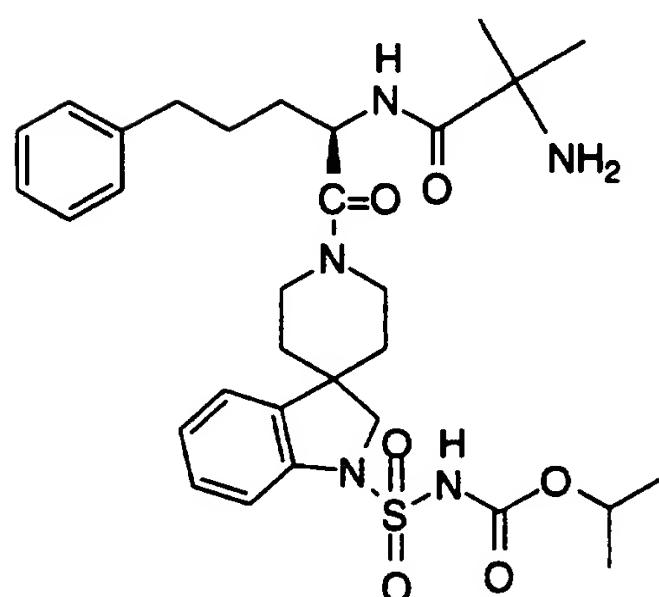
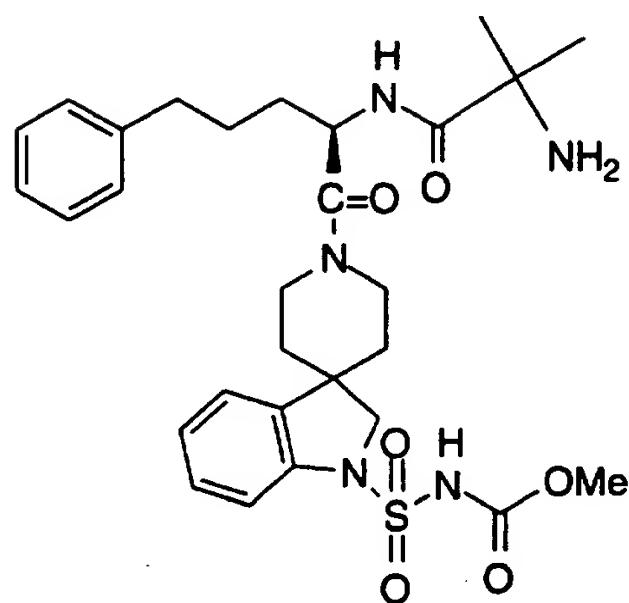
m is 0, 1, or 2;

and the pharmaceutically acceptable salts and individual diastereomers thereof.

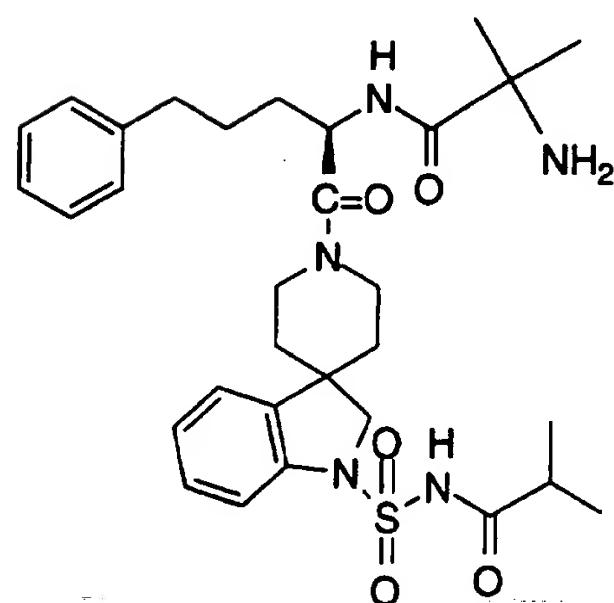
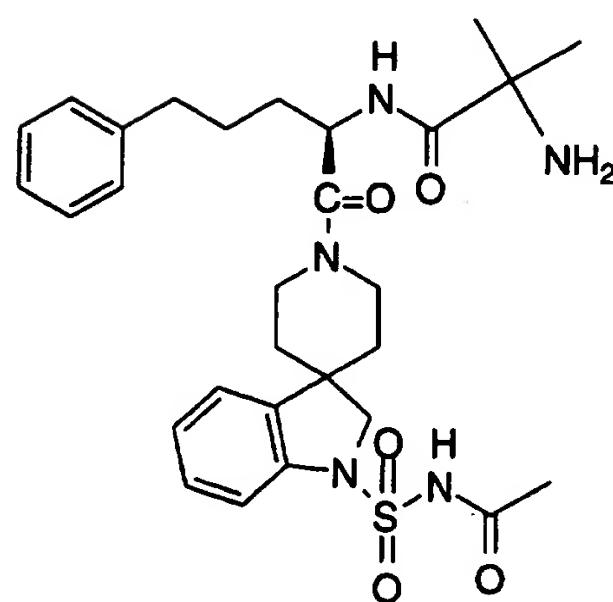
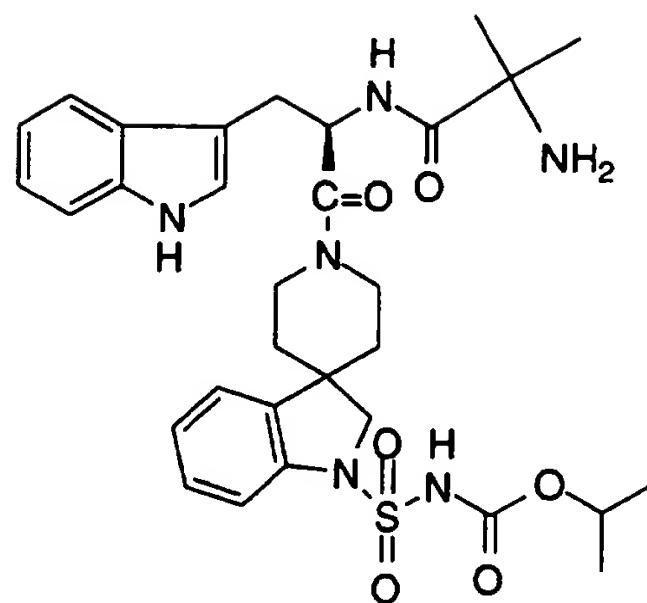
30

- 70 -

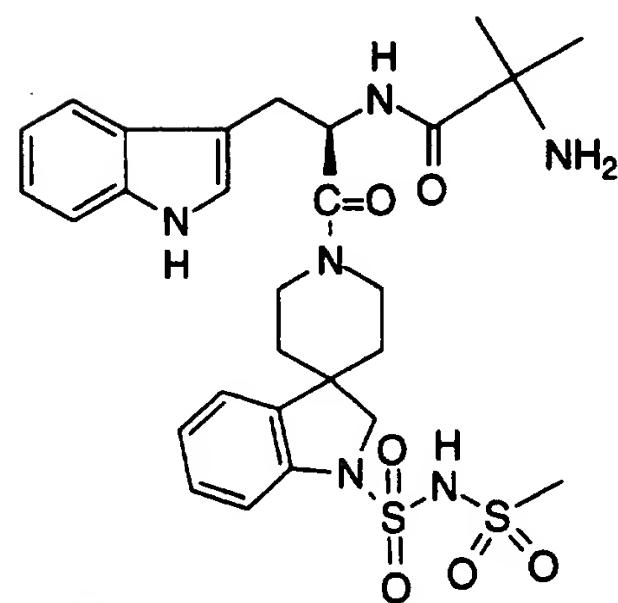
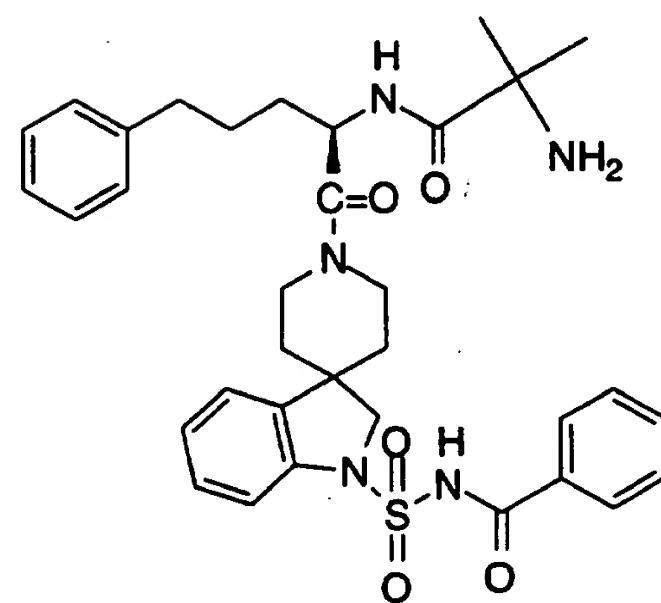
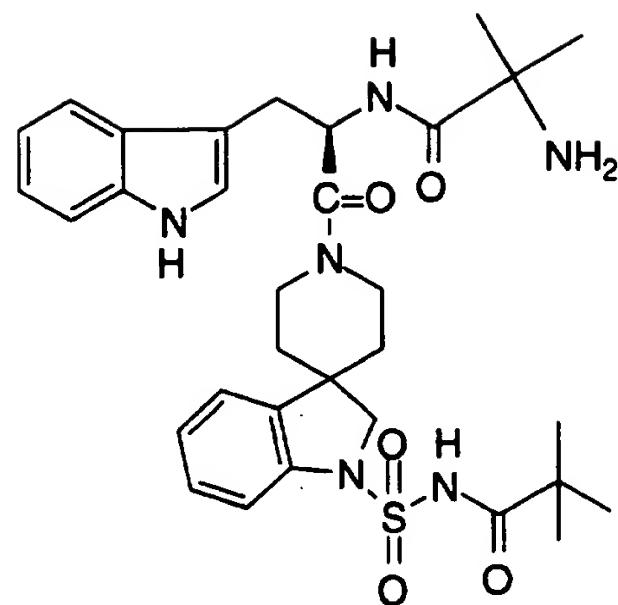
4. A compound which is selected from the group consisting of:



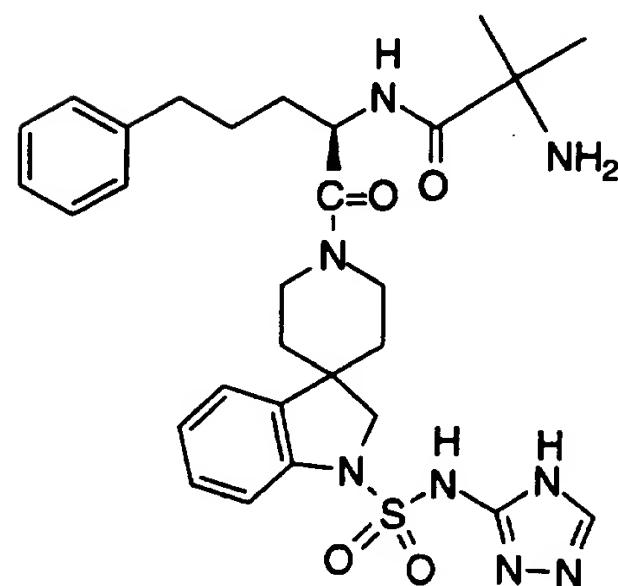
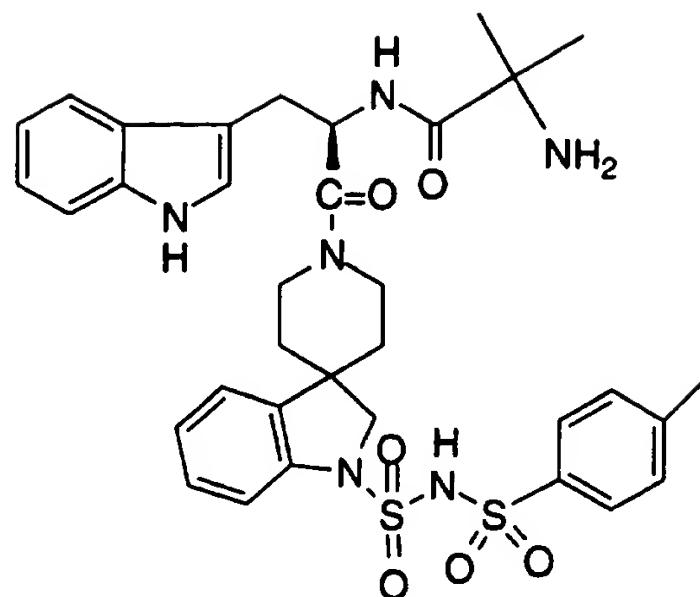
- 71 -



- 72 -



- 73 -



or a pharmaceutically acceptable salt thereof.

- 74 -

5. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

6. A pharmaceutical composition useful for increasing
5 the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an additional growth hormone secretagogue.

10 7. The pharmaceutical composition of Claim 6 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

15 8. A pharmaceutical composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and a compound of Claim 1.

9. The pharmaceutical composition of Claim 8 wherein
20 the bisphosphonate compound is alendronate.

10. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a
25 compound of Claim 1.

11. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an
30 effective amount of a compound of Claim 1.

- 75 -

12. A method for the treatment of a disease or a condition which is benefited by the anabolic effects of enhanced growth hormone levels that comprises administering to a patient in need thereof an effective amount a compound of Claim 1.

5

13. The method of Claim 12 wherein the disease or condition is selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and the treatment of patients recovering from major surgery, wounds or burns.

15

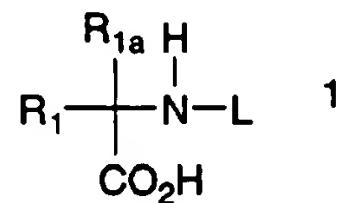
14. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and a compound of Claim 1.

20

15. The method of Claim 14 wherein the bisphosphonate compound is alendronate.

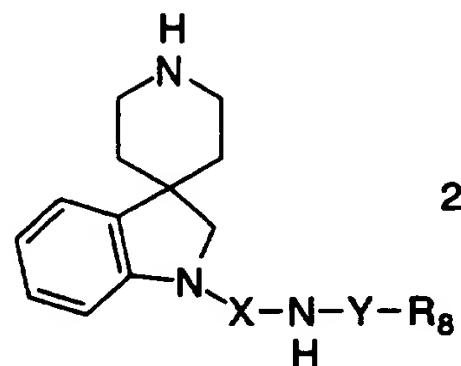
- 76 -

16. A process for the preparation of a compound of
Claim 1 which comprises reacting a compound (1) of the formula:

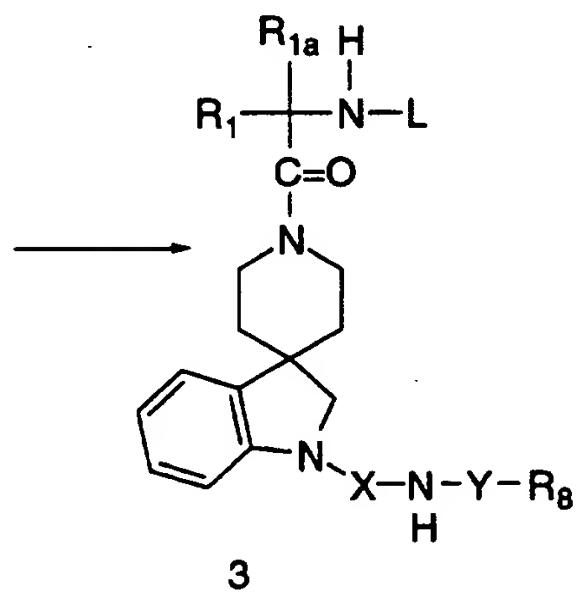


5

wherein L is an amino protecting group,
with a compound (2) of the formula:



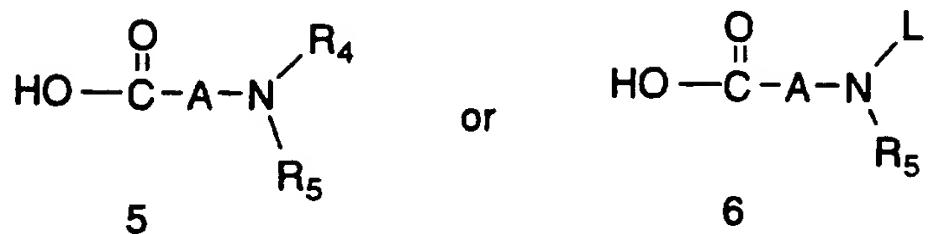
to give a compound (3) of the formula:



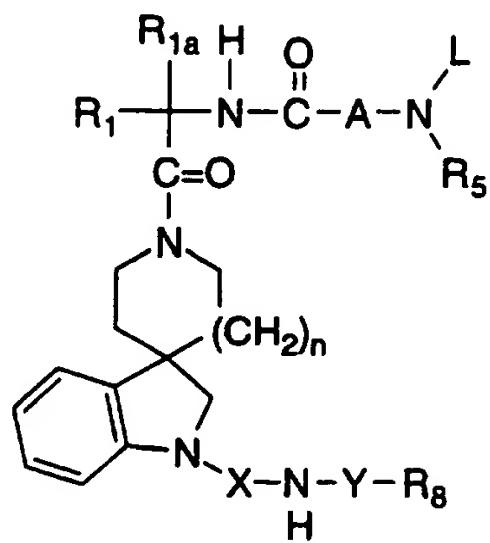
and thereafter removing the amino protecting group L;

- 77 -

then reacting the product therefrom with an amino acid (5) or (6) of the formula:



to give a compound (7) of the formula:



followed by removal of the amino protecting group L, if present, to give the compound of Claim 1.

AMENDED CLAIMS

[received by the International Bureau on 15 December 1995 (15.12.95);
original claim 1 amended; remaining claims unchanged (1 page)]

Z is -N(R9)- or -O-, wherein R9 is hydrogen or C₁-C₆ alkyl;

R₁₀ and R_{10a} are independently selected from the group consisting of:
hydrogen, -C₁-C₆ alkyl, trifluoromethyl, phenyl, and substituted C₁-C₆

5 alkyl wherein the substituents are selected from the group consisting of:
imidazolyl, phenyl, indolyl, naphthyl, p-hydroxyphenyl, -OR₂,
-S(O)_mR₂, -C(O)OR₂, -C₃-C₇ cycloalkyl, -N(R₂)(R₂), and
-C(O)N(R₂)(R₂);
or R₁₀ and R_{10a} are optionally independently joined to one or both of
10 R₄ and R₅ groups to form an alkylene bridge between the terminal
nitrogen and the alkyl portion of the R₁₀ or R_{10a} groups, wherein the
bridge contains 1 to 5 carbons atoms;

R₈ is hydrogen, C₁-C₁₀ alkyl, phenyl, benzyl or diphenyl methyl

15 wherein the phenyl, benzyl or diphenyl groups may be substituted by
halo, methyl or OR₂;

X is SO₂;

20 Y is selected from: SO₂, CO, C(O)O, C(O)N(R₂), and SO₂N(R₂);

m is 0, 1, or 2; and

n is 1 or 2;

25 and pharmaceutically acceptable salts and individual diastereomers
thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/08854

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 401/00 451/00; A01N 43/42

US CL : 546/17; 514/278

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/17; 514/278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 94/13696 (MERCK AND CO.) 23 JUNE 1994, page 5	1-16
Y	EP, A, 513,974, (MERCK AND CO.) 19 NOVEMBER 1992, entire document	12-14
Y	EP, A, 144,230, (PFIZER LIMITED) 12 JUNE 1985, entire document	12,13

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:		
•A• document defining the general state of the art which is not considered to be of particular relevance	•T• later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
•E• earlier document published on or after the international filing date	•X• document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
•L• document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	•Y• document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
•O• document referring to an oral disclosure, use, exhibition or other means	•&• document member of the same patent family	
•P• document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
05 OCTOBER 1995

Date of mailing of the international search report

15 NOV 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230Authorized Officer
CYNTHIA HARRIS jd

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/08854

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- I. Claims 1-10, 11, and 16, drawn to compounds, compositions containing compounds and process for preparing compounds
- II. Claims 12-15, drawn to methods for using the compounds

The inventions I & II lack the same or corresponding technical feature for the following reasons: The groupings contain different methods of use, 37 CFR 1.475(d).

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest



The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.